PSJ15 Exh 4

Form Approved: OMB No. 0910-0001, Expiration Date: May 31, 2008, See OMB Statement on Page 3.

TRANSMITTAL OF ADVERTISEMENTS AND PROMOTIONAL LABELING FOR DRUGS AND BIOLOGICS FOR HUMAN USE

1. DATE SUBMITTED: 04/06/2009

2 LABEL REVIEW NO. *(Biologics)*

3. NDA/ANDA/AADA OR BLA/PLA/PMA Number: 77-142
Single product ☐ Multiple products ☒
For multiple products, submit completed form and specimen of advertising/promotional materials to one application of choice and attach separate sheet addressing items 3-5 for remainder of products. Refer to No. 3 on instruction sheet.

NOTE: Form 2253 is required by law. Reports are required for approved NDAs and ANDAs (21 CFR 314.81)

4. PROPRIETARY NAME
Methadone Hydrochloride Tablets USP (Dispersible, Orange Flavored)

5. ESTABLISHED NAME
Methadone Hydrochloride Tablets for Oral Suspension USP
Prod. Code No. 2540

6. PACKAGE INSERT DATE and ID NO
(Latest final printing labeling)
041107

7. MANUFACTURER NAME:
Mallinckrodt Inc.
License No. N/A
(Biologics)

FDA/CBER USE ONLY

REVIEWED BY:	DATE	RETURNED BY:	DATE

8. **ADVERTISMENT / PROMOTIONAL LABLEING MATERIALS**

Please check only one: ☒ Professional ☐ Consumer

Material Type (use FDA codes) a.	Dissemination/ Publication Date b.	Applicant's Material ID Code and/or description c.	Previous review No. if applicable / date (PLA Submissions) d.	COMMENTS:
PCT	4/6/2009	HA123 – "Addiction Treatment Product Catalog - March 2009" – Product Catalog to provide information about Addiction Treatment products for clinics		

9. TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Celeste M. Reisch, Global Labeling Manager

10. SIGNATURE OF RESPONSIBLE OFFICIAL
Celeste M Reisch

11. APPLICANT'S RETURN ADDRESS
Mallinckrodt Inc.
675 McDonnell Boulevard
Hazelwood, MO 63042

12. RESPONSIBLE OFFICIAL'S
a. PHONE NO.
(314) 654-3120
b. FAX NO.
(314) 654-3140

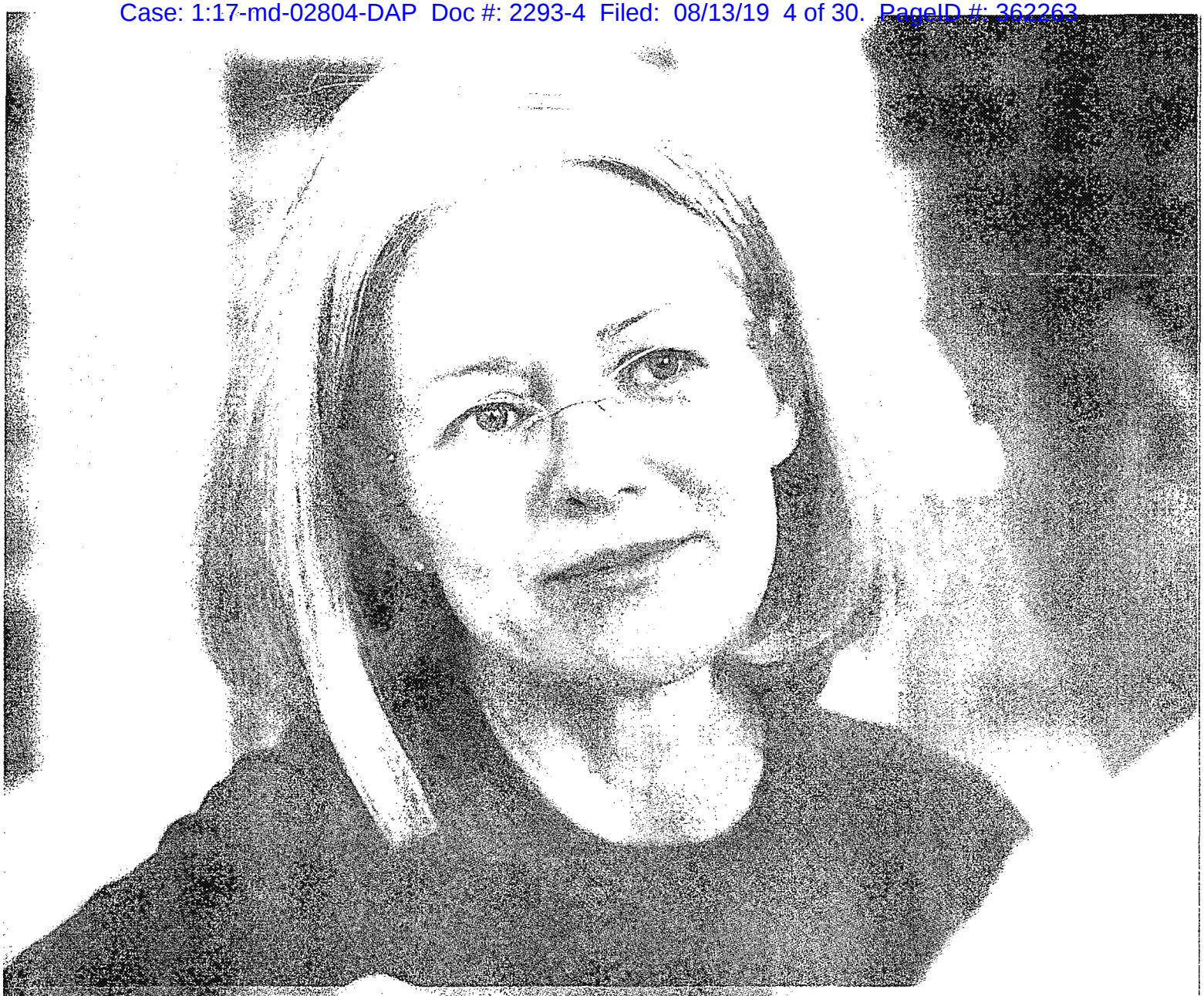
13. FOR CBER PRODUCTS ONLY: *(Check One)*
☐ Part I/Draft ☐ Part II/Final

FORM FDA 2253 (10/07) PREVIOUS EDITION IS OBSOLETE. PSC Graphics: (301) 443-1090 EF

Transmittal of Advertisements dated April 6, 2009

"Addiction Treatment Product Catalog – March 2009"

3. NDA/ANDA/ AADA No.:	4. PROPRIETARY NAME:	5. ESTABLISHED NAME:	5.a PRODUCT CODE:	6. PACKAGE INSERT REVISION:
17-116	Methadose™ Oral Concentrate and Methadose™ Sugar-Free Oral Concentrate	Methadone Hydrochloride Oral Concentrate USP and Methadone Hydrochloride Oral Concentrate USP	0527 (10 mg/mL) 8725 (10 mg/mL)	101507
40-050	Methadose™ Oral Tablets	Methadone Hydrochloride Tablets USP	6974 (5 mg) 3454 (10 mg)	120506
74-184	Methadose™ Dispersible Tablets	Methadone Hydrochloride Tablets for Oral Suspension USP	0540 (40 mg)	041107
06-383	Methadone Hydrochloride USP Powder	Methadone Hydrochloride USP Powder	7113 (50 mg) 7115 (100 mg)	July 1998



Addiction Treatment Product Catalog

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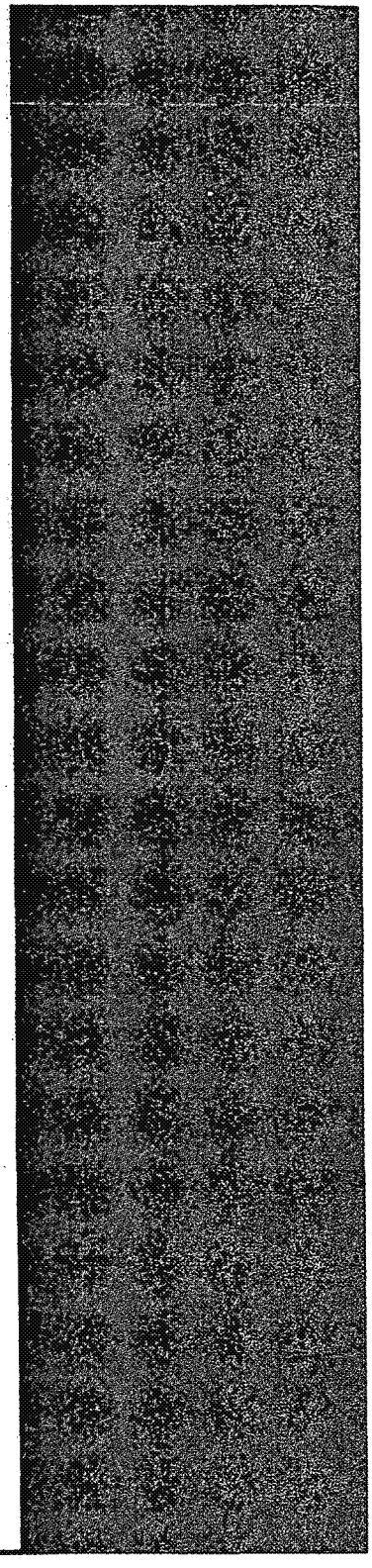
ADDICTION TREATMENT – A COLLABORATIVE EFFORT



Methadone Hydrochloride

Deaths, cardiac and respiratory, have been reported during initiation and conversion of pain patients to methadone treatment from treatment with other opioid agonists. It is critical to understand the pharmacokinetics of methadone when converting patients from other opioids. Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration. Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration. In addition, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

These products are indicated for detoxification treatment of opioid addiction (heroin or other morphine-like drugs) and for maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services. Methadone treatment for analgesic therapy in patients with acute or chronic pain should only be initiated if the potential analgesic or palliative care benefit of treatment with methadone is considered and outweighs the risks. Methadone is contraindicated in patients with a known hypersensitivity to methadone hydrochloride or any other ingredient in Methadone Hydrochloride tablets for oral suspension. Methadone is contraindicated in any situation where opioids are contraindicated such as: patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings), and in patients with acute bronchial asthma or hypercarbia. Methadone is contraindicated in any patient who has or is suspected of having a paralytic ileus.

NDC #00406	Product Description	Size	Case Quantity	DEA Schedule	Tablet Shape/ Color
METHADONE HYDROCHLORIDE TABLETS, USP (DISPERSIBLE, ORANGE FLAVORED)					
2540-01	Methadone Hydrochloride Tablets, USP (Dispersible, Orange Flavored) (Methadone Hydrochloride Tablets for Oral Suspension, USP) 40 mg	100	6	C II	
METHADOSE™ ORAL CONCENTRATE					
0527-10	Methadose™ Oral Concentrate 10 mg per mL (methadone hydrochloride oral concentrate, USP)	1000 mL	4	C II	
8725-10	Methadose™ Sugar-Free Oral Concentrate 10 mg per mL (Dye-Free, Sugar-Free, Unflavored) (methadone hydrochloride oral concentrate, USP)	1000 mL	4	C II	
0525-10	Cherry Flavored Concentrate (Placebo for Methadose™ Oral Concentrate 10 mg per mL)	1000 mL	4	NA	
METHADOSE™ ORAL TABLETS					
6974-34	Methadose™ Oral Tablets 5 mg (methadone hydrochloride tablets, USP) 5	100	12	C II	
3454-34	Methadose™ Oral Tablets 10 mg (methadone hydrochloride tablets, USP) 10 mg	100	12	C II	
0548-34	Methadose™ Dispersible Tablets 40 mg (methadone hydrochloride tablets, USP) 40 mg	100	6	C II	
METHADONE HYDROCHLORIDE, USP POWDER					
1510-56	Methadone Hydrochloride USP Powder	50 gram Bottle	1	C II	
1510-57	Methadone Hydrochloride USP Powder	100 gram Bottle	1	C II	
1510-59	Methadone Hydrochloride USP Powder	500 gram Bottle	1	C II	

Important Information

Mallinckrodt is pleased to provide the above product identification guide for our products. Although every effort has been made to ensure the accuracy of photographs and content, it is important to note that the products have been reduced in size and color may vary slightly. The information presented is to be used only as a reference guide.

If you have specific requests regarding product identification, please call: Medical Information 800.778.7898

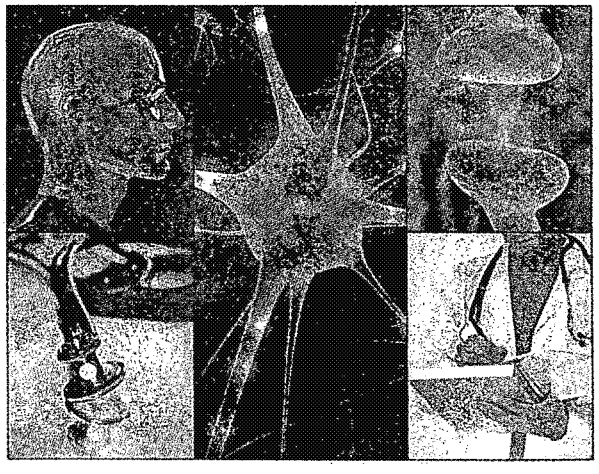
Mallinckrodt MMTP

Methadone Training Program

This training program is a series of in-service education programs on the treatment of opioid addiction and the use of methadone. Suggested audience for this program is MMT clinic healthcare professionals, therapists, counselors, administrators, other staff, and patients and their families.

Seven individual programs are now available exclusively from and conducted by Covidien Mallinckrodt National Accounts Managers.

- The History & Medical Basis of Methadone in the Treatment of Opioid Addiction
- Achieving Adequate Methadone Dosing
- Using Methadone Safely
- Understanding Addiction: The Great Brain Robbery
- The Addicted Brain: A Disease Perspective
- Dual Disorders: Addiction & Mental Illness
- SAM* in MMT (*Substance-Abuse Monitoring)



Contact your Covidien Mallinckrodt National Account Manager to schedule a methadone training program for your clinic.

Mallinckrodt MMTP
Methadone Training Program

History and Medical Basis of Methadone
- Where, when and why was methadone developed?
- How was methadone first used?
- How did it come to be used for treating opioid addiction?
- How does methadone work?
- Why is methadone so effective for treating opioid addiction?

Achieving Adequate Methadone Dosing
- What are the key objectives and phases of methadone maintenance treatment?
- What are the important benefits of an adequate methadone dose?
- How are adequate dose levels assessed?
- Are there special situations that influence methadone effects, and how can these be managed for better outcomes?

Using Methadone Safely
- What is the safety profile of methadone?
- How does opioid tolerance affect safety?
- Are there certain precautions for starting methadone therapy?
- What sort of side effects and adverse reactions might be experienced with methadone?
- How can clinic staff and patients help minimize methadone side effects and adverse reactions?

Understanding Addiction
- How is addiction defined?
- Why are certain drugs addictive?
- How do people become addicted?
- What are some important clinical considerations?

The Addicted Brain
- Why is addiction a brain disease?
- How do addictive substances affect the brain and cause dysfunctions?
- Why do addicted persons continue to self-destruct despite reasons to stop?
- How can medications and psychotherapy help with addiction recovery?

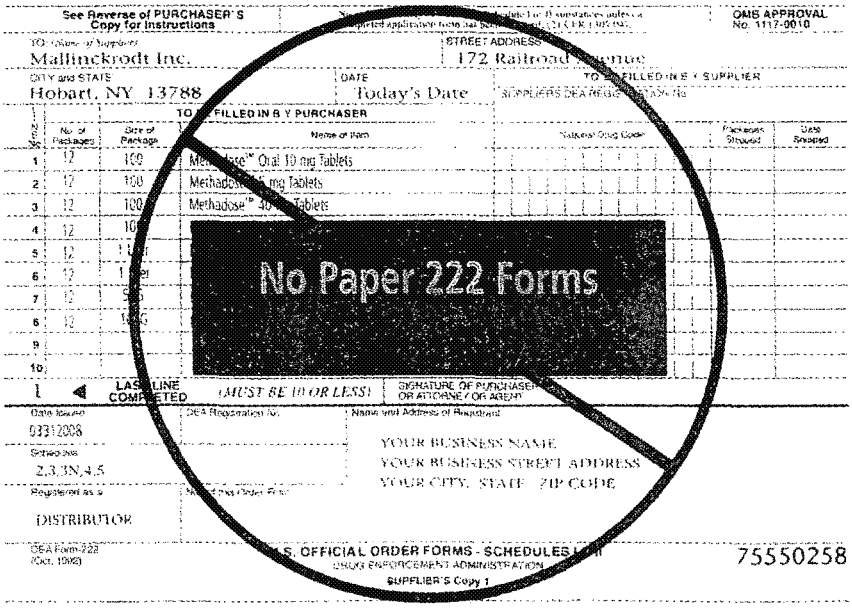
Dual Disorders
- What are dual disorders, and why is diagnosing them so important?
- How prevalent are dual disorders?
- Does methadone itself help or hinder recovery from dual disorders?
- Do dual disorders affect success in MMT?

SAM* in MMT (*Substance-Abuse Monitoring)
- What is SAM?
- Do standards or guidelines exist?
- What is SAM's purpose in MMT?
- When are screens vs. tests used?
- How can SAM benefit patients?

NAADAC Approved Education Provider
Provider #563
CEU Credits Now Available
individual state certification available upon request.

We are pleased to introduce our new online ordering process, designed to simplify order placement and to manage DEA requirements in ordering your Schedule II products for Addiction Treatment.

In partnership with GHX WebConnect and the DEA's Web Trader software, the program allows addiction treatment clinics to place secure, electronic controlled-substances orders and to check the status of shipments without the supporting paper DEA 222 Order Form by using DEA-issued digital certificate technology.



For questions regarding this program, please contact Customer Service at 800.325.8888.

DEA Order Form Preparation

Our customer service representatives are available to assist you in filling out and mailing your DEA 222 Order Forms to purchase Schedule II products. See below for a completed DEA 222 Order Form example.

The following are instructions for completing your DEA 222 Order Form and mailing to Mallinckrodt.

1. Supplier's name and DEA registered address is:
   Mallinckrodt Inc.
   172 Railroad Ave.
   Hobart, NY 13788
2. Current date
3. List items ordered: "No. of Packages," "Size of Package," "Name of Item"
4. DO NOT fill in area marked "TO BE FILLED IN BY SUPPLIER."
5. Fill in "LAST LINE COMPLETED." This number should represent the number of different items listed in the "NAME OF ITEM" column (not the total number of packages and not necessarily the number of lines completed).
6. "SIGNATURE OF PURCHASER" line must be signed by person with legal authority.
7. DO NOT alter printed information in "Name and Address of Registrant" section. If your name or address has changed, contact your Regional DEA Office. Shipment can only be made to the address printed on the DEA 222 Order Form.
8. FEDERAL REGULATIONS DO NOT ALLOW SUPPLIERS TO ACCEPT DEA 222 ORDER FORMS CONTAINING CORRECTIONS, ALTERATIONS OR WRITE-OVERS. If a mistake is made while completing a form, you must VOID the form and issue a new one.
9. The DEA 222 Order Form is mailed to the following address:
   Mallinckrodt Inc.
   Attn: Dosage Pharmaceuticals
   675 McDonnell Blvd.
   Hazelwood, MO 63042

   Mail only the BROWN and GREEN copies of the DEA 222 Order Form to Mallinckrodt. For additional instructions for completing these forms, refer to the back of your BLUE "PURCHASER'S" copy.

See Reverse of PURCHASER'S Copy for Instructions | No order form may be issued for Schedule I or II substances unless a completed application form has been received. (21 CFR 1305.04) | OMB APPROVAL No. 1117-0010

TO: (Name of Supplier): Mallinckrodt Inc.
STREET ADDRESS: 172 Railroad Avenue
CITY and STATE: Hobart, NY 13788
DATE: Today's Date
TO BE FILLED IN B Y SUPPLIER
SUPPLIERS DEA REGISTRATION No.

TO BE FILLED IN B Y PURCHASER

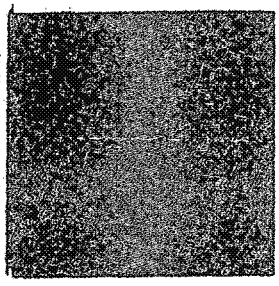
Item No	No. of Packages	Size of Package	Name of Item	National Drug Code	Packages Shipped	Date Shipped
1	12	100	Methadose™ Oral 10 mg Tablets			
2	12	100	Methadose™ 5 mg Tablets			
3	12	100	Methadose™ 40 mg Tablets			
4	12	100	Methadone HCl - 40 mg Orange Tabs			
5	12	1 Liter	Methadose™ Oral Conc - Cherry			
6	12	1 Liter	Methadose™ Sugar Free			
7	12	50G	Methadone HCl USP Powder			
8	12	100G	Methadone HCl USP Powder			
9						
10						

1 ◀ LAST LINE COMPLETED (MUST BE 10 OR LESS) | SIGNATURE OF PURCHASER OR ATTORNEY OR AGENT

Date Issued: 02/12/08
DEA Registration No:
Name and Address of Registrant:
YOUR BUSINESS NAME
YOUR BUSINESS STREET ADDRESS
YOUR CITY, STATE ZIP CODE
Schedules: 2,3,3N,4,5
Registered as a: DISTRIBUTOR
No. of this Order Form:

DEA Form 222 (Oct. 1992) | U.S. OFFICIAL ORDER FORMS - SCHEDULES I & II DRUG ENFORCEMENT ADMINISTRATION SUPPLIER'S Copy 1 | 75550258

Please reference "Mallinckrodt Inc." on DEA Form 222 to ensure efficient processing. (This reference should be made under the "To: (Name of Supplier)" section in the upper left portion of the DEA 222 Form.)



Customer Service

ORDER INFORMATION

Our highly responsive customer service department can assist you in placing your orders by phone, fax, mail and EDI. For assistance with preparing your DEA order form, please see previous page. Please note that all Mallinckrodt products are shipped in case quantities only. Minimum order amount is $300.00.

Customer Service Toll Free No.: 800.325.8888
Fax No.: 314.654.6511
Mailing Address: Mallinckrodt - Customer Service
675 McDonnell Blvd., 10-4-S
Hazelwood, MO 63042

CUSTOMER SERVICE HOURS: Monday through Friday, 7:30 am to 4:30 pm central time

Customer Support Services are available to assist you with billing, credit, returns and shipment schedule inquiries and procedures.

CONCEALED SHIPMENT DAMAGES/LOSSES

Damage/Loss claims must be documented upon delivery and reported directly to Mallinckrodt Customer Service at 800.325.8888 within 10 days of purchase. DEA recommends that all customers open and inventory all shipments as soon as possible. Failure to report these damages/losses in a timely manner significantly impairs Mallinckrodt's ability to properly investigate the cause of the damage or loss. Any damage or loss reported to Mallinckrodt after 10 days of purchase will not be eligible for credit.

MARKETING SERVICES

Our marketing support services are committed to providing you information and answering your inquiries on:

- Product Information
- Bids and Contract Administration
- EDI
- Conventions and Trade Shows

Marketing Services Toll Free No.: 800.833.1717 EXT. 44085
Fax No.: 314.654.8238
Mailing Address: Mallinckrodt - Contracts Dept.
675 McDonnell Blvd., 10-4-S
Hazelwood, MO 63042

To demonstrate our commitment to the services you deserve, Mallinckrodt has installed an automated charge back and rebate system to increase our transaction efficiency and supplier performance with our trading partners. In addition, Mallinckrodt has EDI capabilities and invites our customers to call and establish electronic transaction processing.

SHIPMENTS AND WAREHOUSE FACILITY

Our distribution center is located in our pharmaceuticals manufacturing and packaging facility at 172 Railroad Ave., Hobart, NY, 13788. This shipping facility is a state-of-the-art distribution center which will enhance our daily shipping efficiency and provide better service for our customers' product orders and scheduling needs.

Our distribution center ships products five days a week, Monday through Friday. Methadone products ship to Addiction Treatment clinics Monday through Thursday.

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Mallinckrodt

Return Goods Policy

RETURNABLE ITEMS THAT DO NOT REQUIRE PRE-AUTHORIZATION

- In order to receive credit, Products in original, unopened containers must be returned no earlier than six (6) months prior to the expiration of the Product's shelf life and no later than twelve (12) months after expiration of the Product's shelf life.
- No credit will be given for the return of partial bottles of any Product (unless required by applicable law), however, partial bottles may be returned no earlier than six (6) months prior to expiration of the Product's shelf life and no later than twelve (12) months after expiration of the Product's shelf life.
- All Products must be returned in the original, secured package. **Contact Mallinckrodt Customer Service at 800.325.8888 with any questions.**

PROCEDURES FOR RETURNING PRODUCTS THAT DO NOT REQUIRE PRE-AUTHORIZATION

All returns that do not require pre-authorization must be shipped to the following address:

CapOne™ Returns Program
Mallinckrodt Returns
6101 North 64th Street
Milwaukee, WI 53218
Telephone number: 800.950.5479
Fax number for DEA Form 222 requests: 414.967.3372
E-mail for DEA Form 222 requests: MFGRClientservice@capitalreturns.com

RETURNS THAT REQUIRE PRE-AUTHORIZATION

Products shipped in error or Products damaged in transit must be reported to Mallinckrodt Customer Service at 800.325.8888 within ten (10) days of receipt by the Customer and pre-authorization and instructions relating to the return of those Products must be obtained by Customer from Mallinckrodt Customer Service.

Please reference "Mallinckrodt Inc." on DEA Form 222 to ensure efficient processing. (This reference should be made under the "To: (Name of Supplier)" section in the upper left portion of the DEA 222 Form.)

PRODUCTS THAT ARE NOT RETURNABLE

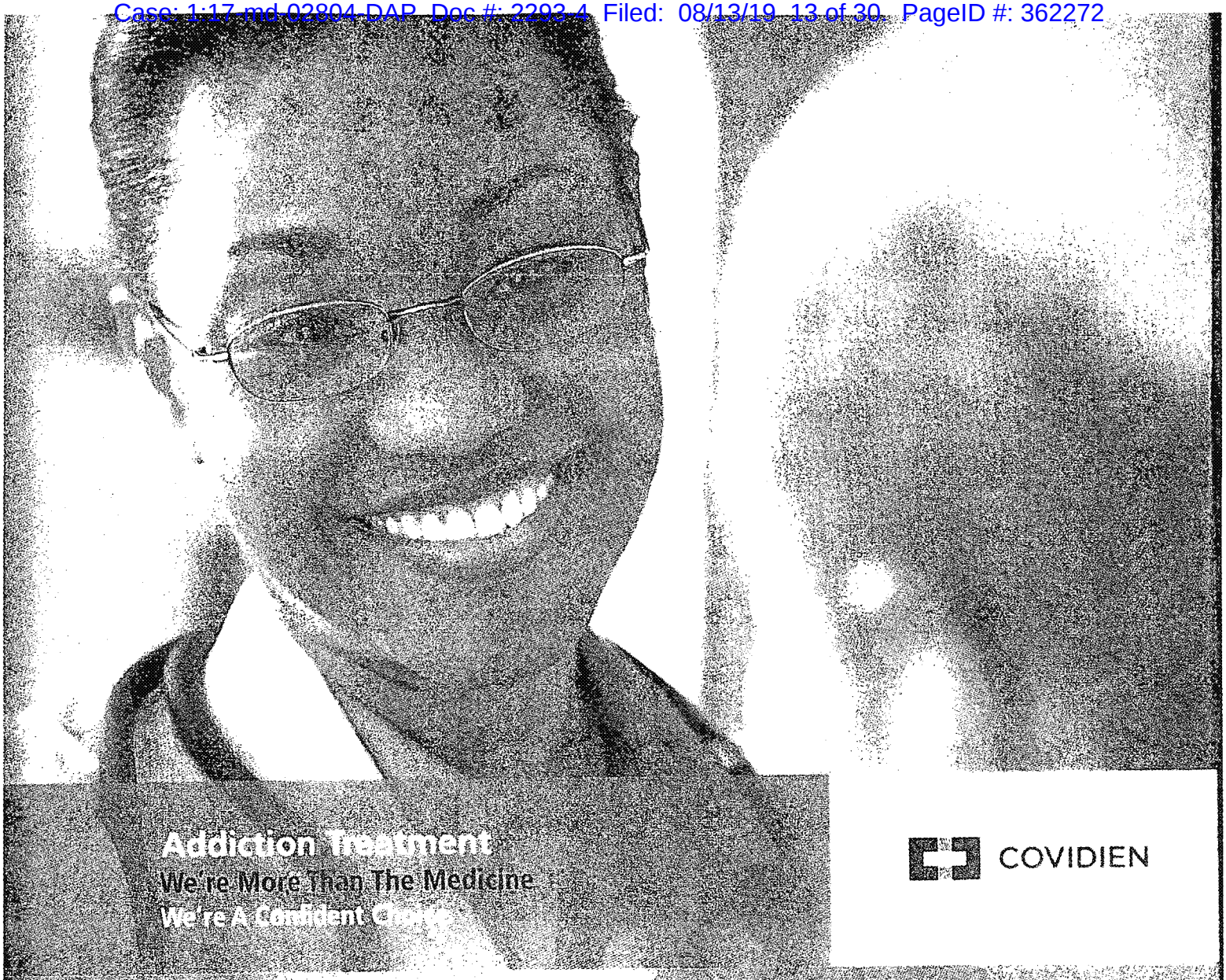
Notwithstanding any of the foregoing, the following Products will not be accepted for return:

- Covidien Imaging Solutions, Covidien Respiratory and Monitoring Solutions, and Mallinckrodt Baker products;
- Products with more than six (6) months remaining shelf life;
- Products retained more than twelve (12) months after expiration of its shelf life;
- Products damaged due to insurable causes or acts of force majeure, or damaged/deteriorated due to improper handling or storage by Customer;
- Products remaining after a bankruptcy, insolvency, liquidation, fire or distress sale;
- Repackaged Products;
- Any Products sold on a non-returnable basis, including, but not limited to, product sold short-dated;
- Products purchased or distributed contrary to federal, state or local laws;
- Products with labels removed or altered;
- Products that have been outside the United States and United States territories;
- Any items designated as samples or free goods.

VALUATION OF RETURNS

- Credit will be issued based on Mallinckrodt's current Returned Goods Pricing Schedule, which is available upon request.
- Contract customers will be issued credit based on current contract price(s) at the time of the return or original invoice price, whichever is lower.
- Mallinckrodt will only credit Products returned to Capital Returns, Inc. (unless Mallinckrodt Customer Service instructs Customer to return the Products in another manner).
- Third party processing fees are not reimbursable.
- Transportation charges, including insurance, are to be prepaid by Customer, except when Products are shipped in error by Mallinckrodt.
- A restocking fee of 20% of the credit will be charged for items ordered in error or for overstock Products. Mallinckrodt has full authority to determine if Product is of an overstock nature.

For questions on this Return Goods Policy, please contact Mallinckrodt Customer Service at 800.325.8888.



Addiction Treatment

We're More Than The Medicine

We're A Confident Choice

COVIDIEN

Notes

A Solid Foundation

- Reliable Supply
- Quality Products
- Excellent Service

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ADDICTION TREATMENT CATALOG 3/2009

CUSTOMER SERVICE
800.325.8888

MEDICAL INFORMATION
800.778.7898

WWW.MALLINCKRODT.COM

SPECIMEN

05400407 Methadone Hydrochloride Tablets for Oral Suspension USP L20M27

METHADOSE® Dispersible Tablets, 40 mg (C II)
(Methadone Hydrochloride Tablets for Oral Suspension USP)
and
Methadone Hydrochloride Tablets USP, 40 mg
(Dispersible, Orange Flavored)
(Methadone Hydrochloride Tablets for Oral Suspension USP)
Rx only
FOR ORAL USE ONLY
(Following Dispersion in a Liquid)

Deaths have been reported during initiation of methadone treatment for opioid dependence. In some cases, drug interactions with other drugs, both licit and illicit, have been suspected. However, in other cases, deaths appear to have occurred *due to the respiratory or cardiac effects of methadone and too-rapid* titration without appreciation for the accumulation of methadone over time. It is critical to understand the pharmacokinetics of methadone and to exercise vigilance during treatment initiation and dose titration (*see* DOSAGE AND ADMINISTRATION). Patients must also be strongly cautioned against self-medicating with CNS depressants during initiation of methadone treatment.

Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) *have been observed during treatment with methadone. Most cases involve* patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Conditions for Distribution and Use of Methadone Products for the Treatment of Opioid Addiction

Code of Federal Regulations, Title 42, Sec 8

Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall *dispense and use methadone in oral form only and according to the treatment* requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment.

Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program approval, and injunction precluding operation of the program.

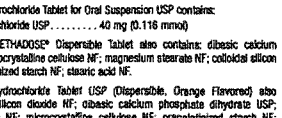
Regulatory Exceptions to the General Requirement for Certification to Provide Opioid Agonist Treatment:

1. During inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21 CFR 1306.07(c)), to facilitate the treatment of the primary admitting diagnosis.
2. During an emergency period of *no* longer than *3 days* while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21 CFR 1306.07(b)).

DESCRIPTION

Methadone hydrochloride tablets for oral suspension USP is for oral administration following dispersion in a liquid. Each tablet contains 40 mg of methadone hydrochloride.

Methadone hydrochloride is chemically described as (3-heptanone, 6-(dimethylamino)-4,4- diphenyl-, hydrochloride). Methadone hydrochloride is a white, essentially odorless, bitter-tasting crystalline powder. It is very soluble in water, soluble in isopropanol and in chloroform, and practically insoluble in ether and in glycerine. It is present in methadone hydrochloride tablets for oral suspension as the racemic mixture. Methadone hydrochloride has a melting point of 235°C, a pKa of 8.25 in water at 20°C, a solution (1 in 100) pH between 4.5 and 6.5, a partition coefficient of 117 at pH 7.4 in octanol/water and a molecular weight of 345.91. Its molecular formula is $C_{21}H_{27}NO{\cdot}HCl$ and its structural formula is:



$C_{21}H_{27}NO \cdot HCl$ MW = 345.91

The tablet preparation of methadone hydrochloride tablets for oral suspension contains insoluble excipients and must not be injected.

Each Methadone Hydrochloride Tablet for Oral Suspension USP contains:

Methadone Hydrochloride USP . . . . . 40 mg (0.116 mmol)

In addition, each METHADOSE® Dispersible Tablet also contains: dibasic calcium phosphate USP; microcrystalline cellulose NF; magnesium stearate NF; colloidal silicon dioxide NF; pregelatinized starch NF; stearic acid NF.

Each *Methadone Hydrochloride Tablet USP* (Dispersible, Orange Flavored) also contains: colloidal silicon dioxide NF; dibasic calcium phosphate dihydrate USP; magnesium stearate NF; microcrystalline cellulose NF; pregelatinized starch NF; stearic acid NF; orange blend: FD&C yellow #6, FD&C yellow #6 laka, and FD&C yellow #5 laka; orange flavor.

CLINICAL PHARMACOLOGY

Mechanism of Action

Methadone hydrochloride is a mu-agonist; a synthetic opioid analgesic with multiple actions qualitatively similar to those of morphine, the most prominent of which involves the central nervous system and organs composed of smooth muscle. The principal therapeutic uses for methadone are analgesia and detoxification or maintenance in opioid addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

Some data also indicate that methadone acts as an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The contribution of NMDA receptor antagonism to methadone's efficacy is unknown. Other NMDA receptor antagonists have been shown to produce neurotoxic effects in animals.

Pharmacokinetics

Absorption

Following oral administration the bioavailability of methadone ranges between 36 to 100% and peak plasma concentrations are achieved between 1 to 7.5 hours. Dose proportionality of methadone pharmacokinetics is not known. However, after administration of daily oral doses ranging from 10 to 225 mg, the steady-state plasma concentrations ranged between 65 to 630 ng/mL and the peak concentrations ranged between 124 to 1255 ng/mL. Effect of food on the bioavailability of methadone has not been evaluated.

Distribution

Methadone is a lipophilic drug and the steady-state volume of distribution ranges between 1.0 to 8.0 L/kg. In plasma, methadone is predominantly bound to α_1-acid glycoprotein (85% to 90%). Methadone is secreted in saliva, breast milk, amniotic fluid and umbilical cord plasma.

Metabolism

Methadone is primarily metabolized by N-demethylation to an inactive metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP). Cytochrome P450 enzymes, primarily CYP3A4, CYP2B6, CYP2C19, and to a lesser extent CYP2C9 and CYP2D6, are responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in the urine.

Excretion

The elimination of methadone is mediated by extensive biotransformation, followed by renal and fecal excretion. Published reports indicate that after multiple dose administration the apparent plasma clearance of methadone ranged between 1.4 to 126 L/h, and the terminal half-life ($T_{\frac{1}{2}}$) was highly variable and ranged between 8 to 59 hours in different studies. Since methadone is lipophilic, it has been known to persist in the liver and other tissues. The slow release from the liver and other tissues may prolong the duration of methadone action despite low plasma concentrations.

Pharmacokinetics in Special Populations

Pregnancy

The disposition of oral methadone has been studied in approximately 30 pregnant patients in the 2nd and 3rd trimesters. Elimination of methadone was significantly changed in pregnancy. Total body clearance of methadone was increased in pregnant patients compared to the same patients postpartum or to non-pregnant opioid-dependent women. The terminal half-life of methadone is decreased during 2nd and 3rd trimesters. The decrease in plasma half-life and increased clearance of methadone resulting in lower methadone trough levels during pregnancy can lead to withdrawal symptoms in some pregnant patients. The dosage may need to be increased or the dosing interval decreased in pregnant patients receiving methadone (*see* **PRECAUTIONS: Pregnancy, Labor and Delivery,** *and* **DOSAGE AND ADMINISTRATION**).

Renal Impairment

Methadone pharmacokinetics have not been extensively evaluated in patients with renal insufficiency. Unmetabolized methadone and its metabolites are excreted in urine to a variable degree. Methadone is a basic (pKa=9.2) compound and the pH of the urinary tract can alter its disposition in plasma. Urine acidification has been shown to increase renal elimination of methadone. Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for increasing the *elimination of methadone or its metabolites.*

Hepatic Impairment

Methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized by hepatic pathways, therefore patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

Gender

The pharmacokinetics of methadone have not been evaluated for gender specificity.

Race

The pharmacokinetics of methadone have not been evaluated for race specificity.

Geriatric

The pharmacokinetics of methadone have not been evaluated in the geriatric population.

Pediatric

The pharmacokinetics of methadone have not been evaluated in the pediatric population.

Drug Interactions (*see* PRECAUTIONS: Drug Interactions)

Methadone undergoes hepatic N-demethylation by cytochrome P-450 isoforms, *principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6.* Coadministration of methadone with inducers of these enzymes may result in more rapid methadone metabolism, and potentially, decreased effects of methadone. Conversely, administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects. Pharmacokinetics of methadone may be unpredictable when coadministered with drugs that are known to both induce and inhibit CYP enzymes. Although antiretroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, *lopinavir+ritonavir combination are known to inhibit some CYPs,* they are shown to reduce the plasma levels of methadone, possibly due to their CYP induction activity. Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy before making a dosage adjustment.

INDICATIONS AND USAGE

1. For detoxification treatment of opioid addiction (heroin or other morphine-like drugs).
2. For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

Note – Outpatient maintenance and outpatient detoxification treatment may be provided only by Opioid Treatment Programs (OTPs) certified by the Federal Substance Abuse and Mental Health Services Administration (SAMHSA) and registered by the Drug Enforcement Administration (DEA). This does not preclude the maintenance treatment of a patient with concurrent opioid addiction who is hospitalized for conditions other than opioid addiction and who requires temporary maintenance during the critical period of his/her stay, or of a patient whose enrollment has been verified in a program which has been certified for maintenance treatment with methadone.

CONTRAINDICATIONS

Methadone hydrochloride tablets for oral suspension is contraindicated in patients with a known hypersensitivity to methadone hydrochloride or any other ingredient in methadone hydrochloride tablets for oral suspension.

Methadone is contraindicated in any situation where opioids are contraindicated such as: patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings), and in patients with acute bronchial asthma or hypercarbia.

Methadone is contraindicated in any patient who has or is suspected of having a paralytic ileus.

WARNINGS

Respiratory Depression

Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, in the short-term use setting. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

Respiratory depression is of particular concern in elderly or debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Methadone should be administered with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, and central nervous system (CNS) depression or coma. In these patients, even usual therapeutic doses of methadone may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. Methadone should be used at the lowest effective dose and only under careful medical supervision.

Cardiac Conduction Effects

This information is intended to alert the prescriber to comprehensively evaluate the risks and benefits of methadone treatment. The intent is not to deter the appropriate use of methadone in patients with a history of cardiac disease.

Laboratory studies, both *in vivo* and *in vitro*, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (*torsades de pointes*) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (>200 mg/day). Although most cases involve patients being treated for pain with large, multiple daily doses of methadone, cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. In most of the cases seen at typical maintenance doses, concomitant medications and/or clinical conditions such as hypokalemia were noted as contributing factors. However, *the evidence strongly suggests that methadone* possesses the potential for adverse cardiac conduction effects in some patients.

Methadone should be administered with particular caution to patients already at risk for development of prolonged QT interval (e.g., cardiac hypertrophy, concomitant diuretic use, hypokalemia, hypomagnesemia). Careful monitoring is recommended when using methadone in patients with a history of cardiac conduction abnormalities, those taking medications affecting cardiac conduction, and in other cases where history or physical exam suggest an increased risk of dysrhythmia. QT prolongation has also been reported in patients with no prior cardiac history who have received high doses of methadone. Patients developing QT prolongation while on methadone treatment should be evaluated for the presence of modifiable risk factors, such as concomitant medications with cardiac effects, drugs which might cause electrolyte abnormalities and drugs which might act as inhibitors of methadone metabolism.

The potential risks of methadone, including the risk of life-threatening arrhythmias, should be weighed against the risks of discontinuing methadone treatment. In the patient being treated for opiate dependence with methadone maintenance therapy, these risks include a very high likelihood of relapse to illicit drug use following methadone discontinuation.

The use of methadone in patients already known to have a prolonged QT interval has not been systematically studied. The potential risks of methadone should be weighed against *the substantial morbidity and mortality associated with untreated opioid* addiction.

In using methadone an individualized benefit to risk assessment should be carried out and should include evaluation of patient presentation and complete medical history. For patients judged to be at risk, careful monitoring of cardiovascular status, including evaluation of QT prolongation and dysrhythmias should be performed.

Incomplete Cross-Tolerance between Methadone and Other Opioids

Patients tolerant to other opioids may be incompletely tolerant to methadone. Incomplete cross-tolerance is of particular concern for patients tolerant to other mu-opioid agonists who are being converted to methadone, thus making determination of dosing during opioid conversion complex. Deaths have been reported during conversion from chronic, high-dose treatment with other opioid agonists. A high degree of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise.

Misuse, Abuse, and Diversion of Opioids

Methadone is a mu-agonist opioid with an abuse liability similar to that of morphine and other opioid agonists and is a Schedule II controlled substance. Methadone, like morphine and other opioids used for analgesia, has the potential for being abused and is subject to criminal diversion.

Methadone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing methadone hydrochloride tablets for oral suspension in situations where the clinician is concerned about an increased risk of misuse, abuse, or diversion. Abuse of methadone poses a risk of overdose and death. This risk is increased with concurrent abuse of methadone with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Other CNS Depressants

Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS *depressants (including alcohol)* concomitantly with methadone may experience respiratory depression, hypotension, profound sedation, or coma (*see* **PRECAUTIONS**).

Interactions with Alcohol and Drugs of Abuse

Methadone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression. Deaths associated with illicit use of methadone frequently have involved concomitant benzodiazepine abuse.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, opioids produce effects which may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution, and only if it is deemed essential.

Acute Abdominal Conditions

The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Hypotensive Effect

The administration of methadone may result in severe hypotension in patients whose ability to maintain normal blood pressure is compromised (e.g., severe volume depletion).

PRECAUTIONS

Methadone hydrochloride tablets for oral suspension should be used with caution in *elderly and debilitated patients; patients who are known to be sensitive to central* nervous system depressants, such as those with cardiovascular, pulmonary, renal, or hepatic disease; and in patients with comorbid conditions or concomitant medications which may predispose to dysrhythmia or reduced ventilatory drive.

Drug Interactions

In vitro results suggest that methadone undergoes hepatic N-demethylation by cytochrome P450 enzymes, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6. Coadministration of methadone with inducers of these enzymes may result in a more rapid metabolism and potential for decreased effects of methadone, whereas administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects. Although antiretroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir+ritonavir combination are known to inhibit CYPs, they are shown to reduce the plasma levels of methadone, possibly due to their CYP induction activity. Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy.

Opioid Antagonists, Mixed Agonist/Antagonists, and Partial Agonists

As with other mu-agonists, patients maintained on methadone may experience withdrawal symptoms when given opioid antagonists, mixed agonist/antagonists, and partial agonists. Examples of such agents are naloxone, naltrexone, pentazocine, nalbuphine, butorphanol, and buprenorphine.

Anti-Retroviral Agents

Abacavir, Amprenavir, Efavirenz, Nelfinavir, Nevirapine, Ritonavir, Lopinavir+Ritonavir Combination – Coadministration of these anti-retroviral agents resulted in increased clearance or decreased plasma levels of methadone. Methadone-maintained patients beginning treatment with these antiretroviral drugs should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly.

Didanosine and Stavudine – Experimental evidence demonstrated that methadone decreased the AUC and peak levels for didanosine and stavudine, with a more significant decrease for didanosine. Methadone disposition was not substantially altered.

Zidovudine – Experimental evidence demonstrated that methadone increased the area under the concentration-time curve (AUC) of zidovudine which could result in toxic effects.

Cytochrome P450 Inducers

Methadone-maintained patients beginning treatment with CYP3A4 inducers should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly. The following drug interactions were reported following coadministration of methadone with inducers of cytochrome P450 enzymes:

Rifampin – In patients well-stabilized on methadone, concomitant administration of rifampin resulted in a marked reduction in serum methadone levels and a concurrent appearance of withdrawal symptoms.

Phenytoin – In a pharmacokinetic study with patients on methadone maintenance therapy, phenytoin administration (250 mg b.i.d. initially for 1 day followed by 300 mg QD for 3 to 4 days) resulted in an approximately 50% reduction in methadone exposure and withdrawal symptoms occurred concurrently. Upon discontinuation of phenytoin, the incidence of withdrawal symptoms decreased and methadone exposure increased to a level comparable to that prior to phenytoin administration.

St. John's Wort, Phenobarbital, Carbamazepine – Administration of methadone along with other CYP3A4 inducers may result in withdrawal symptoms.

Cytochrome P450 Inhibitors

Since the metabolism of methadone is mediated primarily by CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of methadone. The expected clinical results would be increased or prolonged opioid effects. Thus, methadone-treated patients coadministered strong inhibitors of CYP3A4, such as azole antifungal agents (e.g., ketoconazole) and macrolide antibiotics (e.g., erythromycin), with methadone should be carefully monitored and dosage adjustment should be undertaken if warranted. Some selective serotonin reuptake inhibitors (SSRIs) *(e.g., sertraline, fluvoxamine) may increase methadone plasma levels upon* coadministration with methadone and result in increased opiate effects and/or toxicity.

Voriconazole – Repeat dose administration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 4 days) increased the C_{max} and AUC of (R)-methadone by 31% and 47%, respectively, in subjects receiving a methadone maintenance dose (30 to 100 mg QD). The C_{max} and AUC of (S)-methadone increased by 65% and 103%, respectively. Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed.

Others

Monoamine Oxidase (MAO) Inhibitors – Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving monoamine oxidase *inhibitors or those who have received such agents within 14 days. Similar reactions thus* far have not been reported with methadone. However, if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small, incremental doses of methadone are administered over the course of several hours while the patient's condition and vital signs are under careful observation.

Desipramine – Blood levels of desipramine have increased with concurrent methadone administration.

Potentially Arrhythmogenic Agents

Extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone. Pharmacodynamic interactions may occur with concomitant use of methadone and potentially arrhythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers.

Caution should also be exercised when treating methadone patients concomitantly with drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia) that may prolong the QT interval. These drugs include diuretics, laxatives, and, in rare cases, mineralocorticoid hormones.

Interactions with Alcohol and Drugs of Abuse

Methadone may be expected to have additive effects when used in conjunction with alcohol, other opioids or CNS depressants, or with illicit drugs that cause central nervous system depression. Deaths have been reported when methadone has been abused in conjunction with benzodiazepines.

Anxiety – Since methadone as used by tolerant patients at a constant maintenance dosage does not act as a tranquilizer, patients who are maintained on this drug will react to life problems and stresses with the same symptoms of anxiety as do other individuals. The physician should not confuse such symptoms with those of narcotic abstinence and should not attempt to treat anxiety by increasing the dose of methadone. The action of methadone in maintenance treatment is limited to the control of narcotic withdrawal symptoms and is ineffective for relief of general anxiety.

Acute Pain – Maintenance patients on a stable dose of methadone who experience physical trauma, postoperative pain or other acute pain cannot be expected to derive analgesia from their existing dose of methadone. Such patients should be administered *analgesics, including opioids, in doses that would otherwise be indicated for non-*methadone-treated patients with similar painful conditions. Due to the opioid tolerance induced by methadone, when opioids are required for management of acute pain in methadone patients, somewhat higher and/or more frequent doses will often be required than would be the case for non-tolerant patients.

Physical Dependence

Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence is expected during opioid agonist therapy of opioid addiction.

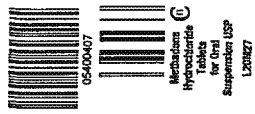
If a physically dependent patient abruptly discontinues use of methadone, or the dose of methadone does not adequately "cover" the patient, an opioid abstinence or withdrawal syndrome may develop and is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. *Other symptoms may also develop, including irritability, anxiety, backache,* joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids may also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms (*see* **PRECAUTIONS: Pregnancy, Labor and Delivery**).

In general, opioids should not be abruptly discontinued (*see* **DOSAGE AND ADMINISTRATION: For Medically Supervised Withdrawal After a Period of Maintenance Treatment**).

Special-Risk Patients

Methadone should be given with caution, and the initial dose reduced, in certain patients such as the elderly and debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture.



The usual precautions should be observed and the possibility of respiratory depression requires added vigilance.

Information for Patients

- Patients should be cautioned that methadone, like all opioids, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving or operating machinery.
- Patients should be cautioned that methadone, like other opioids, may produce orthostatic hypotension in ambulatory patients.
- Patients should be cautioned that alcohol and other CNS depressants may produce an additive CNS depression when taken with this product and should be avoided.
- Patients should be instructed to seek medical attention immediately if they experience symptoms suggestive of an arrhythmia (such as palpitations, dizziness, lightheadedness, or syncope) when taking methadone.
- Patients initiating treatment with methadone should be reassured that the dose of methadone will "hold" for longer periods of time as treatment progresses.
- Patients should be instructed to keep methadone in a secure place out of the reach of children and other household members. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death.
- Patients should be advised not to change the dose of methadone without consulting their physician.
- Women of childbearing potential who become or are planning to become pregnant should be advised to consult their physician regarding the effects of methadone use during pregnancy on themselves and their unborn child.
- If a physically dependent patient abruptly discontinues use of methadone, an opioid abstinence or withdrawal syndrome may develop. If cessation of therapy is indicated, it may be appropriate to taper the methadone dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
- Patients seeking to discontinue treatment with methadone for opioid dependence should be apprised of the high risk of relapse to illicit drug use associated with discontinuation of methadone maintenance treatment.
- Patients should be advised that methadone is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
- Methadone hydrochloride tablets for oral suspension is for oral administration only and must be initially dispersed in liquid before use. After dispersion in liquid, the preparation must not be injected.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis – The results of carcinogenicity assessment in B6C2F1 mice and Fischer 344 rats following dietary administration of two doses of methadone HCl have been published. Mice consumed 15 mg/kg/day or 60 mg/kg/day methadone for two years. These doses were approximately 0.6 and 2.5 times a human daily oral dose of 120 mg/day on a body surface area basis (mg/m²). There was a significant increase in pituitary adenomas in female mice treated with 15 mg/kg/day but not with 60 mg/kg/day. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in male rats. Due to decreased food consumption in males at the high dose, male rats consumed 16 mg/kg/day and 26 mg/kg/day of methadone for two years. These doses were approximately 1.3 and 2.3 times a human daily oral dose of 120 mg/day, based on body surface area comparison. In contrast, female rats consumed 46 mg/kg/day or 88 mg/kg/day for two years. These doses were approximately 3.7 and 7.1 times a human daily oral dose of 120 mg/day, based on body surface area comparison. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in either male or female rats.

Mutagenesis – There are several published reports on the potential genetic toxicity of methadone. Methadone tested negative in tests for chromosome breakage and disjunction and sex-linked recessive lethal gene mutations in germ cells of *Drosophila* using feeding and injection procedures. In contrast, methadone tested positive in the *in vivo* mouse dominant lethal assay and the *in vivo* mammalian spermatogonial chromosome aberration test. Additionally, methadone tested positive in the *E. coli* DNA repair system and *Neurospora crassa* and mouse lymphoma forward mutation assays.

Fertility – Reproductive function in human males may be decreased by methadone treatment. Reductions in ejaculate volume and seminal vesicle and prostate secretions have been reported in methadone-treated individuals. In addition, reductions in serum testosterone levels and sperm motility, and abnormalities in sperm morphology have been reported. Published animal studies provide additional data indicating that methadone treatment of males can alter reproductive function. Methadone produces a significant regression of sex accessory organs and testes of male mice and rats. Additional data have been published indicating that methadone treatment of male rats (once a day for three consecutive days) increased embryolethality and neonatal mortality. Examination of uterine contents of methadone-naive female mice bred to methadone-treated mice indicated that methadone treatment produced an increase in the rate of preimplantation deaths in all post-meiotic states.

Pregnancy

Teratogenic Effects. *Pregnancy Category C* – There are no controlled studies of methadone use in pregnant women that can be used to establish safety. However, an expert review of published data on experiences with methadone use during pregnancy by the Teratogen Information System (TERIS) concluded that maternal use of methadone during pregnancy as part of a supervised, therapeutic regimen is unlikely to pose a substantial teratogenic risk (quantity and quality of data assessed as "limited to fair"). However, the data are insufficient to state that there is no risk (TERIS, last reviewed October, 2002). Pregnant women involved in methadone maintenance programs have been reported to have significantly improved prenatal care leading to significantly reduced incidence of obstetric and fetal complications and neonatal morbidity and mortality when compared to women using illicit drugs. Several factors complicate the interpretation of investigations of the children of women who take methadone during pregnancy. These include the maternal use of illicit drugs, other maternal factors such as nutrition, infection, and psychosocial circumstances, limited information regarding dose and duration of methadone use during pregnancy, and the fact that most maternal exposure appears to occur after the first trimester of pregnancy. Reported studies have generally compared the benefit of methadone to the risk of untreated addiction to illicit drugs.

Methadone has been detected in amniotic fluid and cord plasma at concentrations proportional to maternal plasma and in newborn urine at lower concentrations than corresponding maternal urine.

A retrospective series of 101 pregnant, opiate-dependent women who underwent inpatient opiate detoxification with methadone did not demonstrate any increased risk of miscarriage in the second trimester or premature delivery in the third trimester.

Several studies have suggested that infants born to narcotic-addicted women treated with methadone during all or part of pregnancy have been found to have decreased fetal growth with reduced birth weight, length, and/or head circumference compared to controls. This growth deficit does not appear to persist into later childhood. However, children born to women treated with methadone during pregnancy have been shown to demonstrate mild but persistent deficits in performance on psychometric and behavioral tests.

Additional information on the potential risks of methadone may be derived from animal data. Methadone does not appear to be teratogenic in the rat or rabbit models. However, following large doses, methadone produced teratogenic effects in the guinea pig, hamster and mouse. One published study in pregnant hamsters indicated that a single *subcutaneous dose of methadone ranging from 31 to 185 mg/kg (the 31 mg/kg dose is* approximately 2 times a human daily oral dose of 120 mg/day on a mg/m² basis) on day 8 of gestation resulted in a decrease in the number of fetuses per litter and an increase in the percentage of fetuses exhibiting congenital malformations described as exencephaly, cranioschisis, and "various other lesions". The majority of the doses tested also resulted in maternal death. In another study, a single subcutaneous dose of 22 to 24 mg/kg methadone (estimated exposure was approximately equivalent to a human daily oral dose of 120 mg/day on a mg/m² basis) administered on day 9 of gestation in mice also produced exencephaly in 11% of the embryos. However, no effects were reported in rats and rabbits at oral doses up to 40 mg/kg (estimated exposure was approximately 3 and 6 times, respectively, a human daily oral dose of 120 mg/day on a mg/m² basis) administered during days 6 to 15 and 6 to 18, respectively.

Nonteratogenetic Effects – Babies born to mothers who have been taking opioids regularly prior to delivery may be physically dependent. Onset of withdrawal symptoms in infants is usually in the first days after birth. Withdrawal signs in the newborn include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the maternal dose or the duration of maternal exposure. The duration of the withdrawal signs may vary from a few days to weeks or even months. There is no consensus on the appropriate management of infant withdrawal.

There are conflicting reports on whether SIDS occurs with an increased incidence in infants born to women treated with methadone during pregnancy.

Abnormal fetal nonstress tests (NSTs) have been reported to occur more frequently *when the test is performed 1 to 2 hours after a maintenance dose of methadone in late* pregnancy compared to controls.

Published animal data have reported increased neonatal mortality in the offspring of male rodents that were treated with methadone prior to mating. In these studies, the female rodents were not treated with methadone, indicating paternally-mediated developmental toxicity. Specifically, methadone administered to the male rat prior to mating with methadone-naive females resulted in decreased weight gain in progeny after weaning. The male progeny demonstrated reduced thymus weights, whereas the female progeny demonstrated increased adrenal weights. Furthermore, behavioral testing of these male and female progeny revealed significant differences in behavioral tests compared to control animals, suggesting that paternal methadone exposure can produce physiological and behavioral changes in progeny in this model. Other animal studies have reported that perinatal exposure to opioids including methadone alters neuronal development and behavior in the offspring. Perinatal methadone exposure in rats has been linked to alterations in learning ability, motor activity, thermal regulation, nociceptive responses and sensitivity to drugs. Additional animal data demonstrates evidence for neurochemical changes in the brains of methadone-treated offspring, including changes to the cholinergic, dopaminergic, noradrenergic and serotonergic systems. Additional studies demonstrated that methadone treatment of male rats for 21 to 32 days prior to mating with methadone-naive females did not produce any adverse effects, suggesting that prolonged methadone treatment of the male rat resulted in tolerance to the developmental toxicities noted in the progeny. Mechanistic studies in this rat model suggest that the developmental effects of "paternal" methadone on the progeny appear to be due to decreased testosterone production. These animal data mirror the reported clinical findings of decreased testosterone levels in human males on methadone maintenance therapy for opioid addiction and in males receiving chronic intraspinal opioids.

Clinical Pharmacology for Pregnancy – Pregnant women appear to have significantly lower trough plasma methadone concentrations, increased plasma methadone clearance, and shorter methadone half-life than after delivery. Dosage adjustment using higher doses or administering the daily dose in divided doses may be necessary in *pregnant women treated with methadone (see CLINICAL PHARMACOLOGY and* DOSAGE AND ADMINISTRATION).

Methadone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used. Methadone is not recommended for obstetric analgesia because its long duration of action increases the probability of respiratory depression in the newborn. Narcotics with mixed agonist-antagonist properties should not be used for pain control during labor in patients chronically treated with methadone as they may precipitate acute withdrawal.

Nursing Mothers

Methadone is secreted into human milk. The safety of breast-feeding while taking oral methadone is controversial. At maternal oral doses of 10 to 80 mg/day, methadone concentrations from 50 to 570 mcg/L in milk have been reported, which, in the majority of samples, were lower than maternal serum drug concentrations at steady state. Peak methadone levels in milk occur approximately 4 to 5 hours after an oral dose. Based on an average milk consumption of 150 mL/kg/day, an infant would consume approximately 17.4 mcg/kg/day which is approximately 2 to 3% of the oral maternal dose. Methadone has been detected in very low plasma concentrations in some infants whose mothers were taking methadone. Women on high dose methadone maintenance, who are already breast-feeding, should be counseled to wean breast-feeding gradually in order to prevent neonatal abstinence syndrome.

Methadone-treated mothers considering nursing an opioid-naïve infant should be counseled regarding the presence of methadone in breast milk.

Because of the potential for serious adverse reactions in nursing infants from methadone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother, and weighing the risk of methadone against the risk of maternal illicit drug use.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients and caregivers should be instructed to keep methadone in a secure place out of the reach of children and to discard unused methadone in such a way that individuals other than the patient for whom it was originally prescribed will not come in contact with the drug.

Geriatric Use

Clinical studies of methadone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently compared to younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Renal Impairment

The use of methadone has not been extensively evaluated in patients with renal insufficiency.

Hepatic Impairment

The use of methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized in the liver and patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

Gender

The use of methadone has not been evaluated for gender specificity.

ADVERSE REACTIONS

Heroin Withdrawal

During the induction phase of methadone maintenance treatment, patients are being withdrawn from heroin and may therefore show typical withdrawal symptoms, which should be differentiated from methadone-induced side effects. They may exhibit some or all of the following signs and symptoms associated with acute withdrawal from heroin or other opiates: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, goose-flesh, fever, chilliness alternating with flushing, restlessness, irritability, weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss.

Initial Administration

The initial methadone dose should be carefully titrated to the individual. Too rapid titration for the patient's sensitivity is more likely to produce adverse effects.

The major hazards of methadone are respiratory depression and, to a lesser degree, systemic hypotension. Respiratory arrest, shock, cardiac arrest, and death have occurred.

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses are advisable.

Other adverse reactions include the following: (listed alphabetically under each subsection)

Body as a Whole – asthenia (weakness), edema, headache

Cardiovascular (*also see* **WARNINGS: Cardiac Conduction Effects**) – *arrhythmias*, bigeminal rhythms, bradycardia, cardiomyopathy, ECG abnormalities, extrasystoles, flushing, heart failure, hypotension, palpitations, phlebitis, QT interval prolongation, syncope, T-wave inversion, tachycardia, torsade de pointes, ventricular fibrillation, ventricular tachycardia

Digestive – abdominal pain, anorexia, biliary tract spasm, constipation, dry mouth, glossitis

Hematologic and Lymphatic – reversible thrombocytopenia has been described in opioid addicts with chronic hepatitis

Metabolic and Nutritional – hypokalemia, hypomagnesemia, weight gain

Nervous – agitation, confusion, disorientation, dysphoria, euphoria, insomnia, seizures

Respiratory – pulmonary edema, respiratory depression (see **WARNINGS: Respiratory Depression**)

Skin and Appendages – pruritis, urticaria, other skin rashes, and rarely, hemorrhagic urticaria

Special Senses – hallucinations, visual disturbances

Urogenital – amenorrhea, antidiuretic effect, reduced libido and/or potency, urinary retention or hesitancy

Maintenance on a Stabilized Dose

During prolonged administration of methadone, as in a methadone maintenance treatment program, there is usually a gradual, yet progressive, disappearance of side effects over a period of several weeks. However, constipation and sweating often persist.

DRUG ABUSE AND DEPENDENCE

Methadone hydrochloride tablets for oral suspension contain methadone, a potent Schedule II opioid agonist. Schedule II opioid substances, which also include hydromorphone, morphine, oxycodone, and oxymorphone, have the highest potential for abuse and risk of fatal overdose due to respiratory depression. **Methadone, like morphine and other opioids used for analgesia, has the potential for being abused and is subject to criminal diversion.**

Abuse of methadone poses a risk of overdose and death. This risk is increased with concurrent abuse of methadone with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV.

Since methadone may be diverted for non-medical use, careful record keeping of ordering and dispensing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Methadone, when used for the treatment of opioid addiction in detoxification or maintenance programs, may be dispensed only by opioid treatment programs certified by the Substance Abuse and Mental Health Services Administration (and agencies, practitioners or institutions by formal agreement with the program sponsor).

Infants born to mothers physically dependent on opioids may also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms (see **PRECAUTIONS: Pregnancy, Labor and Delivery**).

OVERDOSAGE

Signs and Symptoms

Serious overdosage of methadone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal-muscle flaccidity, cold and clammy skin, and sometimes, bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment

Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. If a non-tolerant person, takes a large dose of methadone, effective opioid antagonists are available to counteract the potentially lethal respiratory depression. **The physician must remember, however, that methadone is a long-acting depressant (36 to 48 hours), whereas opioid antagonists act for much shorter periods (one to three hours).** The patient must, therefore, be monitored continuously for recurrence of respiratory depression and may need to be treated repeatedly with the narcotic antagonist. If the diagnosis is correct and respiratory depression is due only to overdosage of methadone, the use of other respiratory stimulants is not indicated.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or cardiovascular depression. In an individual physically dependent on opioids, the administration of the usual dose of an opioid antagonist may precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of the antagonist administered. If antagonists must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

Intravenously administered naloxone or nalmefene may be used to reverse signs of intoxication. Because of the relatively short half-life of naloxone as compared with methadone, repeated injections may be required until the status of the patient remains satisfactory. Naloxone may also be administered by continuous intravenous infusion.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

DOSAGE AND ADMINISTRATION

Methadone differs from many other opioid agonists in several important ways. Methadone's pharmacokinetic properties, coupled with high interpatient variability in its absorption, metabolism, and relative analgesic potency, necessitate a cautious and highly individualized approach to prescribing. **Particular vigilance is necessary *during treatment initiation, during conversion from one opioid to another, and* during dose titration.**

While methadone's duration of analgesic action (typically 4 to 8 hours) in the setting of single-dose studies approximates that of morphine, methadone's plasma elimination half-life is substantially longer than that of morphine (typically 8 to 59 hours vs. 1 to 5 hours). **Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects.** Also, with repeated dosing, methadone may be retained in the liver and then slowly released, prolonging the duration of action despite low plasma concentrations. For these reasons, steady-state plasma concentrations, and full analgesic effects, are usually not attained until 3 to 5 days of dosing. Additionally, incomplete cross-tolerance between mu-opioid agonists makes determination of dosing during opioid conversion complex.

The complexities associated with methadone dosing can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration. **A high degree of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise. Deaths have been reported during conversion to methadone from chronic, high-dose treatment with other opioid agonists and during initiation of methadone treatment of addiction in subjects previously abusing high doses of other agonists.**

Detoxification and Maintenance Treatment of Opiate Dependence

For detoxification and maintenance of opiate dependence methadone should be administered in accordance with the treatment standards cited in 42 CFR Section 8.12, including limitations on unsupervised administration.

Methadone hydrochloride tablets for oral suspension is intended for dispersion in a liquid immediately prior to oral administration of the prescribed dose. The tablets should not be chewed or swallowed before dispersing in liquid. Methadone hydrochloride tablets for oral suspension are cross-scored, allowing for flexible dosage adjustment. Each tablet may be broken or cut in half to yield two 20-mg doses, or in quarters to yield four 10-mg doses.

Prior to administration, the desired dose of methadone hydrochloride tablets for oral suspension should be dispersed in approximately 120 mL (4 ounces) of water, orange juice, Tang®, citrus flavors of Kool-Aid® or other acidic fruit beverage prior to taking. Methadone hydrochloride is very soluble in water, but there are some insoluble excipients that will not entirely dissolve. If residue remains in the cup after initial administration, a small amount of liquid should be added and the resulting mixture administered to the patient.

Induction/Initial Dosing

The initial methadone dose should be administered, under supervision, when there are no signs of sedation or intoxication, and the patient shows symptoms of withdrawal. Initially, a single dose of 20 to 30 mg of methadone will often be sufficient to suppress withdrawal symptoms. The initial dose should not exceed 30 mg. If same-day dosing adjustments are to be made, the patient should be asked to wait 2 to 4 hours for further evaluation, when peak levels have been reached. An additional 5 to 10 mg of methadone may be provided if withdrawal symptoms have not been suppressed or if symptoms reappear. The total daily dose of methadone on the first day of treatment should not ordinarily exceed 40 mg. Dose adjustments should be made over the first week of treatment based on control of withdrawal symptoms at the time of expected peak activity (e.g., 2 to 4 hours after dosing). Dose adjustment should be cautious; deaths have occurred in early treatment due to the cumulative effects of the first several days' dosing. Because methadone hydrochloride tablets for oral suspension can be administered only in 10 mg increments, methadone hydrochloride tablets for oral suspension may not be the appropriate product for initial dosing in many patients. Patients should be reminded that the dose will "hold" for a longer period of time as tissue stores of methadone accumulate.

Initial doses should be lower for patients whose tolerance is expected to be low at treatment entry. Loss of tolerance should be considered in any patient who has not taken opioids for more than 5 days. Initial doses should not be determined by previous treatment episodes or dollars spent per day on illicit drug use.

For Short-term Detoxification

For patients preferring a brief course of stabilization followed by a period of medically supervised withdrawal, it is generally recommended that the patient be titrated to a total daily dose of about 40 mg in divided doses to achieve an adequate stabilizing level. Stabilization can be continued for 2 to 3 days, after which the dose of methadone should be gradually decreased. The rate at which methadone is decreased should be determined separately for each patient. The dose of methadone can be decreased on a daily basis or at 2-day intervals, but the amount of intake should remain sufficient to keep withdrawal symptoms at a tolerable level. In hospitalized patients, a daily reduction of 20% of the total daily dose may be tolerated. In ambulatory patients, a somewhat slower schedule may be needed. Because methadone hydrochloride tablets for oral suspension can be administered only in 10 mg increments, methadone hydrochloride tablets for oral suspension may not be the appropriate product for gradual dose reduction in many patients.

For Maintenance Treatment

Patients in maintenance treatment should be titrated to a dose at which opioid symptoms are prevented for 24 hours, drug hunger or craving is reduced, the euphoric effects of self-administered opioids are blocked or attenuated, and the patient is tolerant to the sedative effects of methadone. Most commonly, clinical stability is achieved at doses between 80 to 120 mg/day.

For Medically Supervised Withdrawal After a Period of Maintenance Treatment

There is considerable variability in the appropriate rate of methadone taper in patients choosing medically supervised withdrawal from methadone treatment. It is generally suggested that dose reductions should be less than 10% of the established tolerance or maintenance dose, and that 10 to 14-day intervals should elapse between dose reductions. Because methadone hydrochloride tablets for oral suspension can be administered only in 10 mg increments, it may not be the appropriate product for gradual dose reduction in many patients. Patients should be apprised of the high risk of relapse to illicit drug use associated with discontinuation of methadone maintenance treatment.

HOW SUPPLIED

Each methadone hydrochloride tablet for oral suspension USP contains 40 mg of methadone hydrochloride USP.

METHADOSE® Dispersible Tablets, 40 mg:

Available as a white, round tablet, debossed with "METHADOSE 40" on one side, a quadrisect on the other.

Bottles of 100 . . . . . NDC 0406-0540-34

Methadone Hydrochloride Tablets USP (Dispersible, Orange Flavored), 40 mg:

Available as a speckled orange colored, rounded rectangular tablet, debossed with "M" over "2540" on one side, a quadrisect on the other with an orange odor.

Bottles of 100 . . . . . NDC 0406-2540-01

Dispense in a tight container (USP) with a child-resistant closure. Methadone hydrochloride tablets for oral suspension, if dispensed, must be packaged in child-resistant containers and kept out of reach of children to prevent accidental ingestion.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

METHADOSE is a registered trademark of Mallinckrodt Inc.

Mallinckrodt Inc.
Hazelwood, MO 63042

Printed in U.S.A.

Rev 041107 rr2 MG #21892

tyco Healthcare

Mallinckrodt

Methadose™ Oral Concentrate
(methadone hydrochloride oral concentrate USP) Ⓒ II

and

Methadose™ Sugar-Free Oral Concentrate
(methadone hydrochloride oral concentrate USP)
dye-free, sugar-free, unflavored

Rx only

FOR ORAL USE ONLY

Deaths have been reported during initiation of methadone treatment for opioid dependence. In some cases, drug interactions with other drugs, both licit and illicit, have been suspected. However, in other cases, deaths appear to have occurred due to the respiratory or cardiac effects of methadone and too-rapid titration without appreciation for the accumulation of methadone over time. It is critical to understand the pharmacokinetics of methadone and to *exercise vigilance during treatment initiation and dose titration (see* DOSAGE AND ADMINISTRATION). Patients must also be strongly cautioned against self-medicating with CNS depressants during initiation of methadone treatment.

Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Conditions for Distribution and Use of Methadone Products for the Treatment of Opioid Addiction

Code of Federal Regulations, Title 42, Sec 8

METHADONE PRODUCTS WHEN USED FOR THE TREATMENT OF OPIOID ADDICTION IN DETOXIFICATION OR MAINTENANCE PROGRAMS, SHALL BE DISPENSED ONLY BY OPIOID TREATMENT PROGRAMS (AND AGENCIES, PRACTITIONERS OR INSTITUTIONS BY FORMAL AGREEMENT *WITH THE PROGRAM SPONSOR) CERTIFIED BY THE SUBSTANCE ABUSE* AND MENTAL HEALTH SERVICES ADMINISTRATION AND APPROVED BY THE DESIGNATED STATE AUTHORITY. CERTIFIED TREATMENT PROGRAMS SHALL DISPENSE AND USE METHADONE IN ORAL FORM ONLY AND ACCORDING TO THE TREATMENT REQUIREMENTS STIPULATED IN THE FEDERAL OPIOID TREATMENT STANDARDS (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment.

FAILURE TO ABIDE BY THE REQUIREMENTS IN THESE REGULATIONS MAY RESULT IN CRIMINAL PROSECUTION, SEIZURE OF THE DRUG SUPPLY, REVOCATION OF THE PROGRAM APPROVAL, AND INJUNCTION PRECLUDING OPERATION OF THE PROGRAM.

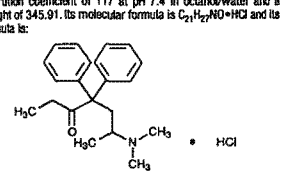
Regulatory Exceptions to the General Requirement for Certification to Provide Opioid Agonist Treatment:

1. During inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21 CFR 1306.07(c)), to facilitate the treatment of the primary admitting diagnosis.
2. During an emergency period of no longer than 3 days while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21 CFR 1306.07(b)).

DESCRIPTION

Methadose™ Oral Concentrate (methadone hydrochloride USP) is supplied as a cherry flavored liquid concentrate. Methadose™ Sugar-Free Oral Concentrate (methadone hydrochloride USP) is a dye-free, sugar-free, unflavored liquid concentrate of methadone hydrochloride. Each liquid concentrate contains 10 mg of methadone hydrochloride per mL.

Methadone hydrochloride is chemically described as 3-heptanone, 6-(dimethylamino)-4, 4-diphenyl-, hydrochloride. Methadone hydrochloride is a white, essentially odorless, bitter-tasting crystalline powder. It is very soluble in water, soluble in isopropanol and in chloroform, and practically insoluble in ether and in glycerine. It is present in Methadose as the racemic mixture. Methadone hydrochloride has a melting point of 235°C, a pKa of 8.25 in water at 20°C, a solution (1 part per 100) pH between 4.5 and 6.5, a partition coefficient of 117 at pH 7.4 in octanol/water and a molecular weight of 345.91. Its molecular formula is $C_{21}H_{27}NO{\cdot}HCl$ and its structural formula is:



Other ingredients of Methadose Oral Concentrate: Artificial cherry flavor, citric acid anhydrous USP, FD&C Red No 40, D&C Red No 33, methylparaben NF, poloxamer 407 NF, propylene glycol USP, propylparaben NF, purified water USP, sodium citrate dihydrate USP, sucrose NF.

Other ingredients of Methadose Sugar-Free Oral Concentrate: Citric acid anhydrous USP, purified water USP, sodium benzoate NF.

CLINICAL PHARMACOLOGY

Mechanism of Action

Methadone hydrochloride is a mu agonist; a synthetic opioid analgesic with multiple actions qualitatively similar to those of morphine, the most prominent of which involves the central nervous system and organs composed of smooth muscle. The principal therapeutic uses for methadone are analgesia and detoxification or maintenance treatment in opioid *addiction. The methadone abstinence syndrome, although qualitatively* similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

Some data also indicate that methadone acts as an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The contribution of NMDA receptor antagonism to methadone's efficacy is unknown. Other NMDA receptor antagonists have been shown to produce neurotoxic effects in animals.

Pharmacokinetics

Absorption

Following oral administration the bioavailability of methadone ranges between 36 to 100% and peak plasma concentrations are achieved between 1 and 7.5 hours. Dose proportionality of methadone *pharmacokinetics is not known.* However, after administration of daily oral doses ranging from 10 to 225 mg, the steady-state plasma concentrations ranged between 65 to 630 ng/mL and the peak concentrations ranged between 124 to 1255 ng/mL. Effect of food on the bioavailability of methadone has not been evaluated.

Distribution

Methadone is a lipophilic drug and the steady-state volume of distribution ranges between 1.0 to 8.0 L/kg. In plasma, methadone is predominantly bound to α_1-acid glycoprotein (85% to 90%). Methadone is secreted in saliva, breast milk, amniotic fluid and umbilical cord plasma.

Metabolism

Methadone is primarily metabolized by N-demethylation to an inactive metabolite, 2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidane (EDDP). Cytochrome P450 enzymes, primarily CYP3A4, CYP2B6, CYP2C19, and to a lesser extent CYP2C9 and CYP2D6, are responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in the urine.

Excretion

The elimination of methadone is mediated by extensive biotransformation, followed by renal and fecal excretion. Published reports indicate that after multiple dose administration the apparent plasma clearance of methadone ranged between 1.4 and 126 L/h, and the terminal half-life ($T_{1/2}$) was highly variable and ranged between 8 and 59 hours in different studies. Since methadone is lipophilic, it has been known to persist in the liver and other tissues. The slow release from the liver and other tissues may prolong the duration of methadone action despite low plasma concentrations.

Pharmacokinetics in Special Populations

Pregnancy

The disposition of oral methadone has been studied in approximately 30 pregnant patients in the second and third trimesters. Elimination of methadone was significantly changed in pregnancy. Total body clearance of methadone was increased in pregnant patients compared to the same patients postpartum or to non-pregnant opioid-dependent women. The terminal half-life of methadone is decreased during second and third trimesters. The decrease in plasma half-life and increased clearance of methadone resulting in lower methadone trough levels during pregnancy can lead to withdrawal symptoms in some pregnant patients. The dosage may need to be increased or the dosing interval decreased in pregnant patients receiving methadone. (See **PRECAUTIONS: Pregnancy, Labor and Delivery,** and **DOSAGE AND ADMINISTRATION.**)

Renal Impairment

Methadone pharmacokinetics have not been extensively evaluated in patients with renal insufficiency. Unmetabolized methadone and its metabolites are excreted in urine to a variable degree. Methadone is a basic (pKa=9.2) compound and the pH of the urinary tract can alter its disposition in plasma. Urine acidification has been shown to increase renal elimination of methadone. Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for increasing the elimination of methadone or its metabolites.

Hepatic Impairment

Methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized by hepatic pathways, therefore *patients with liver impairment may be at risk of accumulating methadone* after multiple dosing.

Gender

The pharmacokinetics of methadone have not been evaluated for gender specificity.

Race

The pharmacokinetics of methadone have not been evaluated for race specificity.

Geriatric

The pharmacokinetics of methadone have not been evaluated in the geriatric population.

Pediatric

The pharmacokinetics of methadone have not been evaluated in the pediatric population.

Drug Interactions (see PRECAUTIONS: Drug Interactions)

Methadone undergoes hepatic N-demethylation by cytochrome P450 isoforms, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6. Coadministration of methadone with inducers of these enzymes may result in more rapid methadone metabolism, and potentially, decreased effects of methadone. Conversely, administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects. Pharmacokinetics of methadone may be unpredictable when coadministered with drugs that are known to both induce and inhibit CYP enzymes. Although anti-retroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir+ritonavir combination are known to inhibit some CYPs, they are shown to reduce the plasma levels of methadone, possibly due to their CYP induction activity. Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy before making a dosage adjustment.

INDICATIONS AND USAGE

1. For detoxification treatment of opioid addiction (heroin or other morphine-like drugs).
2. For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

NOTE

Outpatient maintenance and outpatient detoxification treatment may be provided only by Opioid Treatment Programs (OTPs) certified by the Federal Substance Abuse and Mental Health Services Administration (SAMHSA) and registered by the Drug Enforcement Administration (DEA). This does not preclude the maintenance treatment of a patient with concurrent opioid addiction who is hospitalized for conditions other than opioid addiction and who requires temporary maintenance during the critical period of his/her stay, or of a patient whose enrollment has been verified in a program which has been certified for maintenance treatment with methadone.

CONTRAINDICATIONS

Methadose is contraindicated in patients with a known hypersensitivity to methadone hydrochloride or any other ingredient in Methadose.

Methadose is contraindicated in any situation where opioids are contraindicated such as: patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings), and in patients with acute bronchial asthma or hypercarbia.

Methadone is contraindicated in any patient who has or is suspected of having a paralytic ileus.

WARNINGS

Methadose and Methadose Sugar-Free are for oral administration only. The preparation must not be injected. Methadose and Methadose Sugar-*Free, if dispensed, should be packaged in child-resistant containers and* kept out of reach of children to prevent accidental ingestion.

Respiratory Depression

Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, in the short-term use setting. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

Respiratory depression is of particular concern in elderly or debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may *dangerously decrease pulmonary ventilation.*

Methadone should be administered with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, and central nervous system (CNS) depression or coma. In these patients, even usual therapeutic doses of methadone may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. Methadone should be used at the lowest effective dose and only under careful medical supervision.

Cardiac Conduction Effects

This information is intended to alert the prescriber to comprehensively evaluate the risks and benefits of methadone treatment. The intent is not to deter the appropriate use of methadone in patients with a history of cardiac disease.

Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (> 200 mg/day). Although most cases involve patients being treated for pain with large, multiple daily doses of methadone, cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. In most of the cases seen at typical maintenance doses, concomitant medications and/or clinical conditions such as hypokalemia were noted as contributing factors. However, the evidence strongly suggests that methadone possesses the potential for adverse cardiac conduction effects in some patients.

Methadone should be administered with particular caution to patients already at risk for development of prolonged QT interval (e.g., cardiac hypertrophy, concomitant diuretic use, hypokalemia, hypomagnesemia). Careful monitoring is recommended when using methadone in patients with a history of cardiac conduction abnormalities, those taking medications affecting cardiac conduction, and in other cases where history or physical exam suggest an increased risk of dysrhythmia. QT prolongation has also been reported in patients with no prior cardiac history who have received high doses of methadone. Patients developing QT prolongation while on methadone treatment should be evaluated for the presence of modifiable risk factors, such as concomitant medications with cardiac effects, drugs which might cause electrolyte abnormalities and drugs which might act as inhibitors of methadone metabolism.

The potential risks of methadone, including the risk of life-threatening arrhythmias, should be weighed against the risks of discontinuing methadone treatment. In the patient being treated for opiate dependence with methadone maintenance therapy, these risks include a very high likelihood of relapse to illicit drug use following methadone discontinuation.

The use of methadone in patients already known to have a prolonged QT interval has not been systematically studied. The potential risks of methadone should be weighed against the substantial morbidity and mortality associated with untreated opioid addiction.

When treating patients with methadone, an individualized benefit to risk assessment should be carried out and should include evaluation of patient *presentation and complete medical history. For patients judged to be at* risk, careful monitoring of cardiovascular status, including evaluation of QT prolongation and dysrhythmias should be performed.

Incomplete Cross-tolerance between Methadone and other Opioids

Patients tolerant to other opioids may be incompletely tolerant to methadone. Incomplete cross-tolerance is of particular concern for patients tolerant to other mu-opioid agonists who are being converted to methadone, thus making determination of dosing during opioid conversion complex. Deaths have been reported during conversion from chronic, high-dose treatment with other opioid agonists. A high degree of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise.

Misuse, Abuse, and Diversion of Opioids

Methadone is a mu-agonist opioid with an abuse liability similar to that of morphine and other opioid agonists and is a Schedule II controlled substance. Methadone, like morphine and other opioids used for analgesia, has the potential for being abused and is subject to criminal diversion.

Methadone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when dispensing Methadose in situations where the clinician is concerned about an increased risk of misuse, abuse, or diversion. Abuse of methadone poses a risk of overdose and death. This risk is increased with concurrent abuse of methadone with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with other CNS Depressants

Patients receiving other opioid analgesics, general anesthetics, phenothiazines or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with methadone may experience respiratory depression, hypotension, profound sedation, or coma (see **PRECAUTIONS**).

Interactions with Alcohol and Drugs of Abuse

Methadone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression. Deaths associated with illicit use of methadone frequently have involved concomitant benzodiazepine abuse.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, opioids produce effects which may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution, and only if it is deemed essential.

Acute Abdominal Conditions

The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Hypotensive Effect

The administration of methadone may result in severe hypotension in patients whose ability to maintain normal blood pressure is compromised (e.g., severe volume depletion).

PRECAUTIONS

Methadose should be used with caution in elderly and debilitated patients; patients who are known to be sensitive to central nervous system depressants, such as those with cardiovascular, pulmonary, renal, or hepatic disease; and in patients with comorbid conditions or concomitant medications which may predispose to dysrhythmia or reduced ventilatory drive.

Drug Interactions

In vitro results suggest that methadone undergoes hepatic N-demethylation by cytochrome P450 enzymes, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6. Coadministration of methadone with inducers of these enzymes may result in a more rapid metabolism and potential for decreased effects of methadone, whereas administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects. Although anti-retroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, and lopinavir+ritonavir combination are known to inhibit CYPs, they are shown to reduce the plasma levels of methadone, possibly due to their CYP induction activity. Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy.

Opioid Antagonists, Mixed Agonist/Antagonists, and Partial Agonists

As with other mu-agonists, patients maintained on methadone may experience withdrawal symptoms when given opioid antagonists, mixed agonist/antagonists, and partial agonists. Examples of such agents are naloxone, naltrexone, pentazocine, nalbuphine, butorphanol, and buprenorphine.

Anti-retroviral Agents

Abacavir, amprenavir, efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir+ritonavir combination – Coadministration of these anti-retroviral agents resulted in increased clearance or decreased plasma levels of methadone. Methadone-maintained patients beginning treatment with these anti-retroviral drugs should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly.

Didanosine and Stavudine – Experimental evidence demonstrated that *methadone decreased the area under the concentration-time curve* (AUC) and peak levels for didanosine and stavudine, with a more significant decrease for didanosine. Methadone disposition was not substantially altered.

Zidovudine – Experimental evidence demonstrated that methadone increased the AUC of zidovudine which could result in toxic effects.

Cytochrome P450 Inducers

Methadone-maintained patients beginning treatment with CYP3A4 inducers should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly. The following drug interactions were reported following coadministration of methadone with inducers of cytochrome P450 enzymes:

Rifampin – In patients *well-stabilized* on methadone, concomitant administration of rifampin resulted in a marked reduction in serum methadone levels and a concurrent appearance of withdrawal symptoms.

Phenytoin – In a pharmacokinetic study with patients on methadone maintenance therapy, phenytoin administration (250 mg b.i.d. initially for 1 day followed by 300 mg QD for 3 to 4 days) resulted in an approximately 50% reduction in methadone exposure and withdrawal symptoms occurred concurrently. Upon discontinuation of phenytoin, the incidence of withdrawal symptoms decreased and methadone exposure increased to a level comparable to that prior to phenytoin administration.

St. John's Wort, Phenobarbital, Carbamazepine

Administration of methadone along with other CYP3A4 inducers may result *in withdrawal symptoms.*

Cytochrome P450 Inhibitors

Since the metabolism of methadone is mediated primarily by CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of methadone. The expected clinical results would be increased or prolonged opioid effects. Thus, methadone-treated patients coadministered strong inhibitors of CYP3A4, such as azole antifungal agents (e.g., ketoconazole) and macrolide antibiotics (e.g., erythromycin), should be carefully monitored and dosage adjustment should be undertaken if warranted. Some selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline, fluvoxamine) may increase methadone plasma levels upon coadministration with methadone and result in increased opiate effects and/or toxicity.

Voriconazole – Repeat dose administration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 4 days) increased the C_{max} and AUC of (R)-methadone by 31% and 47%, respectively, in subjects receiving a methadone maintenance dose (30 to 100 mg QD). The C_{max} and AUC of (S)-methadone increased by 65% and 103%, respectively. Increased plasma concentrations of methadone have been associated with toxicity, including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed.

Others

Monoamine Oxidase (MAO) Inhibitors – Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving *monoamine oxidase inhibitors or those who have received such agents* within 14 days. Similar reactions thus far have not been reported with methadone. However, if the use of methadone is necessary in such patients, a sensitivity test should be performed in which incremental doses of methadone are administered over the course of several hours while the patient's condition and vital signs are under careful observation.

Desipramine – Plasma levels of desipramine have increased with concurrent methadone administration.

Potentially Arrhythmogenic Agents

Extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone. Pharmacodynamic interactions may occur with concomitant use of methadone and potentially arrhythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers.

Caution should also be exercised when prescribing Methadose concomitantly with drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia) that may prolong the QT interval. These drugs include diuretics, laxatives, and, in rare cases, mineralocorticoid hormones.

Interactions with Alcohol and Drugs of Abuse

Methadone may be expected to have additive effects when used in conjunction with alcohol, other opioids or CNS depressants, or with illicit drugs that cause central nervous system depression. Deaths have been reported when methadone has been abused in conjunction with benzodiazepines.

Anxiety – Since methadone as used by tolerant patients at a constant maintenance dosage does not act as a tranquilizer, patients will react to life problems and stresses with the same symptoms of anxiety as do other individuals. The physician should not confuse such symptoms with those of narcotic abstinence and should not attempt to treat anxiety by increasing the dose of methadone. The action of methadone in maintenance treatment is limited to the control of narcotic withdrawal symptoms and is ineffective for relief of general anxiety.

Acute Pain – Patients in methadone maintenance treatment for opioid dependence who experience physical trauma, postoperative pain or other acute pain cannot be expected to derive analgesia from their existing dose *of methadone. Such patients should be administered analgesics, including* opioids, in doses that would otherwise be indicated for non-methadone-treated patients with similar painful conditions. Due to the opioid tolerance induced by methadone, when opioids are required for management of acute pain in methadone patients, somewhat higher and/or more frequent doses will often be required than would be the case for non-tolerant patients.

Physical Dependence

Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence is expected during opioid agonist therapy of opioid addiction.

If a physically dependent patient abruptly discontinues use of methadone, or the dose of methadone does not adequately "cover" the patient, an opioid abstinence or withdrawal syndrome may develop and is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms may also develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

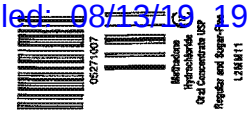
Infants born to mothers physically dependent on opioids may also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms (see **PRECAUTIONS: Pregnancy, Labor and Delivery**).

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: For Medically Supervised Withdrawal After a Period of Maintenance Treatment**).

Special-Risk Patients – *Methadone should be given with caution, and the* initial dose reduced, in certain patients such as the elderly and debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression requires added vigilance.

Information for Patients

- Patients should be cautioned that Methadose, like all opioids, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving or operating machinery.



- Patients who are ambulatory should be cautioned that Methadose, like other opioids, may produce orthostatic hypotension.
- Patients should be cautioned that alcohol and other CNS depressants may produce an additive CNS depression when taken with this product and should be avoided.
- Patients should be instructed to seek medical attention immediately if they experience symptoms suggestive of an arrhythmia (such as palpitations, dizziness, lightheadedness, or syncope) when taking Methadose.
- Patients initiating treatment with Methadose should be reassured that the dose of methadone will "hold" for longer periods of time as treatment progresses.
- Patients should be instructed to keep Methadose in a secure place out of the reach of children and other household members. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death.
- Patients should be advised not to change the dose of Methadose without consulting their physician.
- Women of childbearing potential who become or are planning to become pregnant should be advised to consult their physicians regarding the effects of Methadose use during pregnancy.
- If a physically dependent patient abruptly discontinues use of Methadose, an opioid abstinence or withdrawal syndrome may develop. If cessation of therapy is indicated, it may be appropriate to taper the methadone dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
- Patients seeking to discontinue treatment with Methadose for opioid dependence should be apprised of the high risk of relapse to illicit drug use associated with discontinuation of methadone maintenance treatment.
- *Patients should be advised that Methadose is a potential drug of abuse.* They should protect it from theft, and it should never be taken by anyone other than the individual for whom it was prescribed.
- Breastfeeding:
  1. Methadone use is usually compatible with breastfeeding. Pregnant mothers using methadone should be counseled about the benefits and risks of breastfeeding while using methadone. Counseling should include the following information:
     - The baby receives a small amount of methadone through breastmilk.
     - The baby may experience methadone withdrawal if breastfeeding is discontinued suddenly. Patients discontinuing breastfeeding should develop a plan to wean with the baby's healthcare team.
     - Use of other substances of abuse during breastfeeding will expose the baby to additional risks. Patients who use other substances of abuse should not breastfeed.
  2. When starting methadone for the first time or increasing the dose, breastfeeding patients should watch their babies closely for changes in behavior or breathing patterns.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis – The results of carcinogenicity assessment in B6C2F1 mice and Fischer 344 rats following dietary administration of two doses of methadone HCl have been published. Mice consumed 15 mg/kg/day or 60 mg/kg/day methadone for two years. These doses were approximately 0.6 and 2.5 times a human daily oral dose of 120 mg/day on a body surface area basis (mg/m^2). There was a significant increase in pituitary adenomas in female mice treated with 15 mg/kg/day but not with 60 mg/kg/day. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in male rats. Due to decreased food consumption in males at the high dose, male rats consumed 16 mg/kg/day and 28 mg/kg/day of methadone for two years. These doses were approximately 1.3 and 2.3 times a human daily oral dose of 120 mg/day, based on body surface area comparison. In contrast, female rats consumed 46 mg/kg/day or 88 mg/kg/day for two years. These doses were approximately 3.7 and 7.1 times a human daily oral dose of 120 mg/day, based on body surface area comparison. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in either male or female rats.

Mutagenesis – There are several published reports on the potential genetic toxicity of methadone. Methadone tested negative in tests for chromosome breakage and disjunction and sex-linked recessive lethal gene mutations in germ cells of *Drosophila* using feeding and injection procedures. In contrast, methadone tested positive in the in vivo mouse dominant lethal assay and the in vivo mammalian spermatogonial chromosome aberration test. Additionally, methadone tested positive in the *E.coli* DNA repair system and *Neurospora crassa* and mouse lymphoma forward mutation assays.

Fertility – Reproductive function in human males may be decreased by methadone treatment. Reductions in ejaculate volume and seminal vesicle and prostate secretions have been reported in methadone-treated individuals. In addition, reductions in serum testosterone levels and sperm motility, and abnormalities in sperm morphology have been reported. Published animal studies provide additional data indicating that methadone treatment of males can alter reproductive function. Methadone produces a significant regression of sex accessory organs and testes of male mice and rats. Additional data have been published indicating that methadone treatment of male rats (once a day for three consecutive days) increased embryolethality and neonatal mortality. Examination of uterine contents of methadone-naive female mice bred to methadone-treated mice indicated that methadone treatment produced an increase in the rate of preimplantation deaths in all post-meiotic states.

Pregnancy

Teratogenic Effects – *Pregnancy Category C.* There are no controlled studies of methadone use in pregnant women that can be used to establish safety. However, an expert review of published data on experiences with methadone use during pregnancy by the Teratogen Information System (TERIS) concluded that maternal use of methadone during pregnancy as part of a supervised, therapeutic regimen is unlikely to pose a substantial teratogenic risk (quantity and quality of data assessed as "limited to fair"). However, the data are insufficient to state that there is no risk (TERIS, last reviewed October, 2002). Pregnant women involved in methadone maintenance programs have been reported to have significantly improved prenatal care leading to significantly reduced incidence of obstetric and fetal complications and neonatal morbidity and mortality when compared to women using illicit drugs. Several factors complicate the interpretation of investigations of the children of women who take methadone during pregnancy. These include the maternal use of illicit drugs, other maternal factors such as nutrition, infection, and psychosocial circumstances, limited information regarding dose and duration of methadone use during pregnancy, and the fact that most maternal exposure appears to occur after the first trimester of pregnancy. Reported studies have generally compared the benefit of methadone to the risk of untreated addiction to illicit drugs.

Methadone has been detected in amniotic fluid and cord plasma at concentrations proportional to maternal plasma and in newborn urine at lower concentrations than corresponding maternal urine.

A retrospective series of 101 pregnant, opiate-dependent women who underwent inpatient opiate detoxification with methadone did not demonstrate any increased risk of miscarriage in the second trimester or premature delivery in the third trimester.

Several studies have suggested that infants born to narcotic-addicted women treated with methadone during all or part of pregnancy have been found to have decreased fetal growth with reduced birth weight, length, and/or head circumference compared to controls. This growth deficit does not appear to persist into later childhood. However, children born to women treated with methadone during pregnancy have been shown to demonstrate mild but persistent deficits in performance on psychometric and behavioral tests.

Additional information on the potential risks of methadone may be derived from animal data. Methadone does not appear to be teratogenic in the rat or rabbit models. However, following large doses, methadone produced teratogenic effects in the guinea pig, hamster and mouse. One published study in pregnant hamsters indicated that a single subcutaneous dose of methadone ranging from 31 to 185 mg/kg (the 31 mg/kg dose is approximately twice a human daily oral dose of 120 mg/day on a mg/m^2 basis) on day 8 of gestation resulted in a decrease in the number of fetuses per litter and an increase in the percentage of fetuses exhibiting congenital malformations described as exencephaly, cranioschisis, and "various other lesions." The majority of the doses tested also resulted in maternal death. In another study, a single subcutaneous dose of 22 to 24 mg/kg methadone (estimated exposure was approximately equivalent to a human daily oral dose of 120 mg/day on a mg/m^2 basis) administered on day 9 of gestation *in mice also produced exencephaly in 11% of the embryos.* However, no effects were reported in rats and rabbits at oral doses up to 40 mg/kg (estimated exposure was approximately 3 and 6 times, respectively, a human daily oral dose of 120 mg/day on a mg/m^2 basis) administered during Days 6 to 15 and 6 to 18, respectively.

Nonteratogenetic Effects – Babies born to mothers who have been taking opioids regularly prior to delivery may be physically dependent. Onset of withdrawal symptoms in infants is usually in the first days after birth. Withdrawal signs in the newborn include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the maternal dose or the duration of maternal exposure. The duration of the withdrawal signs may vary from a few days to weeks or even months. There is no consensus on the appropriate management of infant withdrawal.

There are conflicting reports on whether SIDS occurs with an increased incidence in infants born to women treated with methadone during pregnancy.

Abnormal fetal nonstress tests (NSTs) have been reported to occur more frequently when the test is performed 1 to 2 hours after a maintenance dose of methadone in late pregnancy compared to controls.

Published animal data have reported increased neonatal mortality in the offspring of male rats that were treated with methadone prior to mating. In these studies, the female rats were not treated with methadone, indicating paternally-mediated developmental toxicity. Specifically, methadone administered to the male rat prior to mating with methadone-naïve females resulted in decreased weight gain in progeny after weaning. The male progeny demonstrated reduced thymus weights, whereas the female progeny demonstrated increased adrenal weights. Furthermore, behavioral testing of these male and female progeny revealed significant differences in behavioral tests compared to control animals, suggesting that paternal methadone exposure can produce physiological and behavioral changes in progeny in this model. Other animal studies have reported that perinatal exposure to opioids including methadone alters neuronal development and behavior in the offspring. Perinatal methadone exposure in rats has been linked to alterations in learning ability, motor activity, thermal regulation, nociceptive responses and sensitivity to drugs. Additional animal data demonstrates evidence for neurochemical changes in the brains of methadone-treated offspring, including changes to the cholinergic, dopaminergic, noradrenergic and serotonergic systems. Additional studies demonstrated that methadone treatment of male rats for 21 to 32 days prior to mating with methadone-naïve females did not produce any adverse effects, suggesting that prolonged methadone treatment of the male rat resulted in tolerance to the developmental toxicities noted in the progeny. Mechanistic studies in this rat model suggest that the developmental effects of "paternal" methadone on the progeny appear to be due to decreased testosterone production. These animal data mirror the reported clinical findings of decreased testosterone levels in human males on methadone maintenance therapy for opioid addiction and in males receiving chronic intraspinal opioids.

Clinical Pharmacology in Pregnancy – Pregnant women appear to have significantly lower trough plasma methadone concentrations, increased plasma methadone clearance, and shorter methadone half-life than after delivery. Dosage adjustment using higher doses or administering the daily dose in divided doses may be necessary in pregnant women treated with Methadose. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Methadone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used. Methadone is not recommended for obstetric analgesia because its long duration of action increases the probability of respiratory depression in the newborn. Narcotics with mixed agonist-antagonist properties should not be used for pain control during labor in patients chronically treated with methadone as they may precipitate acute withdrawal.

Nursing Mothers

Methadone is secreted into human milk. At maternal oral doses of 10 to 80 mg/day, methadone concentrations from 50 to 570 mcg/L in milk have been reported, which, in the majority of samples, were lower than maternal serum drug concentrations at steady state. Peak methadone levels in milk occur approximately 4 to 5 hours after an oral dose. Based on an average milk consumption of 150 mL/kg/day, an infant would consume approximately 17.4 mcg/kg/day which is approximately 2 to 3% of the oral maternal dose. Methadone has been detected in very low plasma concentrations in some infants whose mothers were taking methadone.

Caution should be exercised when methadone is administered to a nursing woman. There have been rare cases of sedation and respiratory depression in infants exposed to methadone through breast milk.

Mothers using methadone should receive specific information about how to identify respiratory depression and sedation in their babies. They should know when to contact their healthcare provider or seek immediate medical care. A healthcare provider should weigh the benefits of breastfeeding against the risks of infant exposure to methadone and possible exposure to other medicines.

Women being treated with methadone for any indication who are already breastfeeding should be counseled to wean breastfeeding gradually in order to prevent the development of withdrawal symptoms in the infant.

Methadone Maintenance Treatment for Opioid Dependence during Breastfeeding

Women on methadone maintenance therapy, who express a desire to breastfeed, should be informed of the risks and benefits of breastfeeding during pregnancy and immediately postpartum. The patient should clearly understand that, while breastfeeding, she should not use illicit substances or any other drug not prescribed by her healthcare provider. She should understand the reasons why use of additional drugs can increase risk to her breastfeeding infant beyond any risk from methadone.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients and caregivers should be instructed to keep Methadose in a secure place out of the reach of children and to discard unused methadone in such a way that individuals other than the patient for whom it was originally prescribed will not come in contact with the drug.

Geriatric Use

Clinical studies of methadone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently compared to younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Renal Impairment

The use of methadone has not been extensively evaluated in patients with renal insufficiency.

Hepatic Impairment

The use of methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized in the liver and patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

Gender

The use of methadone has not been evaluated for gender specificity.

ADVERSE REACTIONS

Heroin Withdrawal

During the induction phase of methadone maintenance treatment, patients are being withdrawn from heroin and may therefore show typical withdrawal symptoms, which should be differentiated from methadone-induced side effects. They may exhibit some or all of the following signs and symptoms associated with acute withdrawal from heroin or other opiates: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, goose-flesh, fever, chilliness alternating with flushing, restlessness, irritability, weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss.

Initial Administration

The initial methadone dose should be carefully titrated to the individual. Too rapid titration for the patient's sensitivity is more likely to produce adverse effects.

The major hazards of methadone are respiratory depression and, to a lesser degree, systemic hypotension. Respiratory arrest, shock, cardiac arrest, and death have occurred.

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses are advisable.

Other adverse reactions include the following: (listed alphabetically under each subsection)

Body as a Whole – asthenia (weakness), edema, headache

Cardiovascular (also see **WARNINGS: Cardiac Conduction Effects**) – arrhythmias, bigeminal rhythms, bradycardia, cardiomyopathy, ECG abnormalities, extrasystoles, flushing, heart failure, hypotension, palpitations, phlebitis, QT interval prolongation, syncope, T-wave inversion, tachycardia, torsade de pointes, ventricular fibrillation, ventricular tachycardia

Digestive – abdominal pain, anorexia, biliary tract spasm, constipation, dry mouth, glossitis

Hematologic and Lymphatic – reversible thrombocytopenia has been described in opioid addicts with chronic hepatitis

Metabolic and Nutritional – hypokalemia, hypomagnesemia, weight gain

Nervous – agitation, confusion, disorientation, dysphoria, euphoria, insomnia, seizures

Respiratory – pulmonary edema, respiratory depression (see **WARNINGS: Respiratory Depression**)

Skin and Appendages – pruritis, urticaria, other skin rashes, and rarely, hemorrhagic urticaria

Special Senses – hallucinations, visual disturbances

Urogenital – amenorrhea, antidiuretic effect, reduced libido and/or potency, urinary retention or hesitancy

Maintenance on a Stabilized Dose – During prolonged administration of methadone, as in a methadone maintenance treatment program, there is *usually a gradual, yet progressive, disappearance of side effects over a* period of several weeks. However, constipation and sweating often persist.

DRUG ABUSE AND DEPENDENCE

Methadose contains methadone, a potent Schedule II opioid agonist. Schedule II opioid substances, which also include hydromorphone, morphine, oxycodone, and oxymorphone, have the highest potential for abuse and risk of fatal overdose due to respiratory depression. **Methadone, like morphine and other opioids used for analgesia, has the potential for being abused and is subject to criminal diversion.**

Abuse of Methadose poses a risk of overdose and death. This risk is increased with concurrent abuse of Methadose with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV.

Since Methadose may be diverted for non-medical use, careful record keeping of ordering and dispensing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Methadose, when used for the treatment of opioid addiction in detoxification or maintenance programs, may be dispensed only by opioid treatment programs certified by the Substance Abuse and Mental Health Services Administration (and agencies, practitioners or institutions by formal agreement with the program sponsor).

Infants born to mothers physically dependent on opioids may also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms (See **PRECAUTIONS; Pregnancy, Labor and Delivery**).

OVERDOSAGE

Signs and Symptoms

Serious overdosage of methadone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal-muscle flaccidity, cold and clammy skin, *and sometimes, bradycardia and hypotension.* In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment

Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. If a non-tolerant person, takes a large dose of methadone, effective opioid antagonists are available to counteract the potentially lethal respiratory depression. **The physician must remember, however, that methadone is a long-acting depressant (36 to 48 hours), whereas opioid antagonists act for much shorter periods (one to three hours).** The patient must, therefore, be monitored continuously for recurrence of respiratory depression and may need to be treated repeatedly with the narcotic antagonist.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or cardiovascular depression. In an individual physically dependent on opioids, the administration of the usual dose of an opioid antagonist may precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of the antagonist administered. If antagonists must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

Intravenously administered naloxone or nalmefene may be used to reverse signs of intoxication. Because of the relatively short half-life of naloxone as compared with methadone, repeated injections may be required until the status of the patient remains satisfactory. Naloxone may also be administered by continuous intravenous infusion.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

DOSAGE AND ADMINISTRATION

Methadone differs from many other opioid agonists in several important ways. Methadone's pharmacokinetic properties, coupled with high interpatient variability in its absorption, metabolism, and relative analgesic potency, necessitate a cautious and highly individualized approach to prescribing. **Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration.**

While methadone's duration of analgesic action (typically 4 to 8 hours) in the setting of single-dose studies approximates that of morphine, methadone's plasma elimination half-life is substantially longer than that of morphine (typically 8 to 59 hours vs. 1 to 5 hours). **Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects.** Also, with repeated dosing, methadone may be retained in the liver and then slowly released, prolonging the duration of action despite low plasma concentrations. For these reasons, steady-state plasma concentrations, and full analgesic effects, are usually not attained until 3 to 5 days of dosing. Additionally, incomplete cross-tolerance between mu-opioid agonists makes determination of dosing during opioid conversion complex.

The complexities associated with methadone dosing can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration. **A high degree of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise. *Deaths have been reported during conversion to methadone from* chronic, high-dose treatment with other opioid agonists and during initiation of methadone treatment of addiction in subjects previously abusing high doses of other agonists.**

Detoxification and Maintenance Treatment of Opiate Dependence

For detoxification and maintenance of opiate dependence methadone should be administered in accordance with the treatment standards cited in 42 CFR Section 8.12, including limitations on unsupervised administration.

Induction/Initial Dosing

The initial methadone dose should be administered, under supervision, when there are no signs of sedation or intoxication, and the patient shows symptoms of withdrawal. Initially, a single dose of 20 to 30 mg of methadone will often be sufficient to suppress withdrawal symptoms. The initial dose should not exceed 30 mg. If same-day dosing adjustments are to be made, the patient should be asked to wait 2 to 4 hours for further evaluation, when peak levels have been reached. An additional 5 to 10 mg of methadone may be provided if withdrawal symptoms have not been suppressed or if symptoms reappear. The total daily dose of methadone on the first day of treatment should not ordinarily exceed 40 mg. Dose adjustments should be made over the first week of treatment based on control of withdrawal symptoms at the time of expected peak activity (e.g., 2 to 4 hours after dosing). Dose adjustment should be cautious; deaths have occurred in early treatment due to the cumulative effects of the first several days' dosing. Patients should be reminded that the dose will "hold" for a longer period of time as tissue stores of methadone accumulate.

Initial doses should be lower for patients whose tolerance is expected to be low at treatment entry. Loss of tolerance should be considered in any patient who has not taken opioids for more than 5 days. Initial doses should not be determined by previous treatment episodes or dollars spent per day on illicit drug use.

For Short-term Detoxification

For patients preferring a brief course of stabilization followed by a period of medically supervised withdrawal, it is generally recommended that the patient be titrated to a total daily dose of about 40 mg in divided doses to achieve an adequate stabilizing level. Stabilization can be continued for 2 *to 3 days, after which the dose of methadone should be gradually* decreased. The rate at which methadone is decreased should be determined separately for each patient. The dose of methadone can be decreased on a daily basis or at 2-day intervals, but the amount of intake should remain sufficient to keep withdrawal symptoms at a tolerable level. In hospitalized patients, a daily reduction of 20% of the total daily dose may be tolerated. In ambulatory patients, a somewhat slower schedule may be needed.

For Maintenance Treatment

Patients in maintenance treatment should be titrated to a dose at which opioid symptoms are prevented for 24 hours, drug hunger or craving is reduced, the euphoric effects of self-administered opioids are blocked or attenuated, and the patient is tolerant to the sedative effects of methadone. Most commonly, clinical stability is achieved at doses between 80 to 120 mg/day.

For Medically Supervised Withdrawal After a Period of Maintenance Treatment

There is considerable variability in the appropriate rate of methadone taper in patients choosing medically supervised withdrawal from methadone treatment. It is generally suggested that dose reductions should be less than 10% of the established tolerance or maintenance dose, and that 10 to 14-day intervals should elapse between dose reductions. Patients should be apprised of the high risk of relapse to illicit drug use associated with discontinuation of methadone maintenance treatment.

HOW SUPPLIED

Methadose™ Oral Concentrate (methadone hydrochloride oral concentrate USP) 10 mg per mL is supplied as a red, cherry-flavored liquid concentrate.

1 Liter Bottle . . . . . NDC 0406-0527-10
15 Liter Bottle . . . . . NDC 0406-0527-15

Methadose™ Sugar-Free Oral Concentrate (methadone hydrochloride oral concentrate USP) 10 mg per mL is supplied as a dye-free, sugar-free, unflavored liquid concentrate.

1 Liter Bottle . . . . . NDC 0406-8725-10
15 Liter Bottle . . . . . NDC 0406-8725-15

Dispense in tight containers, protected from light. Store at 20° to 25° C (68° to 77° F) [see *USP* Controlled Room Temperature].

Mallinckrodt Inc.
Hazelwood, MO 63042 U.S.A.

tyco Healthcare
Mallinckrodt

Rev 101507 rr2 MG #21025

SPECIMEN

METHADOSE® ORAL TABLETS
METHADONE HYDROCHLORIDE TABLETS USP
C II
5 mg, 10 mg
Rx only

Deaths, cardiac and respiratory, have been reported during initiation and conversion of pain patients to methadone treatment from treatment with other opioid agonists. It is critical to understand the pharmacokinetics of methadone when converting patients from other opioids (see DOSAGE AND ADMINISTRATION). Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration.

Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration.

In addition, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.

Methadone treatment for analgesic therapy in patients with acute or chronic pain should only be initiated if the potential analgesic or palliative care benefit of treatment with methadone is considered and outweighs the risks.

Conditions for Distribution and Use of Methadone Products for the Treatment of Opioid Addiction

Code of Federal Regulations, Title 42, Sec 8

Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment.

Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program approval, and injunction precluding operation of the program.

Regulatory Exceptions to the General Requirement for Certification to Provide Opioid Agonist Treatment:

1. During inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21 CFR 1306.07(c)), to facilitate the treatment of the primary admitting diagnosis).
2. During an emergency period of no longer than 3 days while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21 CFR 1306.07(b)).

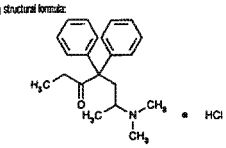
DESCRIPTION

METHADOSE® Oral Tablets (Methadone Hydrochloride Tablets USP), for oral administration, each contain 5 mg or 10 mg of methadone hydrochloride.

Methadone hydrochloride is a white, crystalline material that is water-soluble.

Methadone hydrochloride is chemically described as 6-(dimethylamino)-4,4-diphenyl-3-heptanone hydrochloride. Methadone hydrochloride has a melting point of 235°C, and a pKa of 8.25 in water at 20°C. Its octanol/water partition coefficient at pH 7.4 is 117. A solution (1:100) in water has a pH between 4.5 and 6.5.

It has the following structural formula:



$C_{21}H_{27}NO \cdot HCl$ MW = 345.91

Each tablet also contains Dibasic Calcium Phosphate USP, Microcrystalline Cellulose NF, Magnesium Stearate NF, Colloidal Silicon Dioxide NF, Pregelatinized Starch NF, and Stearic Acid NF.

CLINICAL PHARMACOLOGY

Mechanism of Action

Methadone hydrochloride is a mu-agonist; a synthetic opioid analgesic with multiple actions qualitatively similar to those of morphine, the most prominent of which involves the central nervous system and organs composed of smooth muscle. The principal therapeutic uses for methadone are for analgesia and for detoxification or maintenance in opioid addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

Some data also indicate that methadone acts as an antagonist at the N-methyl-D-aspartate (NMDA) receptor. The contribution of NMDA receptor antagonism to methadone's efficacy is unknown. Other NMDA receptor antagonists have been shown to produce neurotoxic effects in animals.

Pharmacokinetics

Absorption – Following oral administration the bioavailability of methadone ranges between 36 to 100% and peak plasma concentrations are achieved between 1 to 7.5 hours. Dose proportionality of methadone pharmacokinetics is not known. However, after administration of daily oral doses ranging from 10 to 225 mg, the steady-state plasma concentrations ranged between 65 to 630 ng/mL and the peak concentrations ranged between 124 to 1255 ng/mL. Effect of food on the bioavailability of methadone has not been evaluated.

Distribution – Methadone is a lipophilic drug and the steady-state volume of distribution ranges between 1.0 to 8.0 L/kg. In plasma, methadone is predominantly bound to α_1-acid glycoprotein (85% to 90%). Methadone is secreted in saliva, breast milk, amniotic fluid and umbilical cord plasma.

Metabolism – Methadone is primarily metabolized by N-demethylation to an inactive metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). Cytochrome P450 enzymes, primarily CYP3A4, CYP2B6, and CYP2C19 and to a lesser extent CYP2C9 and CYP2D6, are responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in the urine.

Excretion – The elimination of methadone is mediated by extensive biotransformation, followed by renal and fecal excretion. Published reports indicate that after multiple dose administration the terminal half-life ($T_{1/2}$) was highly variable and ranged between 8 to 59 hours in different studies. Since methadone is lipophilic, it has been known to persist in the liver and other tissues. The slow release from the liver and other tissues may prolong the duration of methadone action despite low plasma concentrations.

Pharmacokinetics in Special Populations

Pregnancy – The disposition of oral methadone has been studied in approximately 30 pregnant patients in 2nd and 3rd trimesters. Elimination of methadone was significantly changed in pregnancy. Total body clearance of methadone was increased in pregnant patients compared to the same patients postpartum or to non-pregnant opioid-dependent women. The terminal half-life of methadone is decreased during 2nd and 3rd trimesters. The decrease in plasma half-life and increased clearance of methadone resulting in lower methadone trough levels during pregnancy can lead to withdrawal symptoms in some pregnant patients. The dosage may need to be increased or the dosing interval decreased in pregnant patients receiving methadone (see PRECAUTIONS, Pregnancy, Labor and Delivery, and DOSAGE AND ADMINISTRATION).

Renal Impairment – Methadone pharmacokinetics have not been extensively evaluated in patients with renal insufficiency. Unmetabolized methadone and its metabolites are excreted in urine to a variable degree. Methadone is a basic (pKa=8.2) compound and the pH of the urinary tract can alter its disposition in plasma. Urine acidification has been shown to increase renal elimination of methadone. Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for increasing the elimination of methadone or its metabolites.

Hepatic Impairment – Methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized by hepatic pathways, therefore patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

Gender – The pharmacokinetics of methadone have not been evaluated for gender specificity.

Race – The pharmacokinetics of methadone have not been evaluated for race specificity.

Geriatric – The pharmacokinetics of methadone have not been evaluated in the geriatric population.

Pediatric – The pharmacokinetics of methadone have not been evaluated in the pediatric population.

Drug Interactions (see PRECAUTIONS, Drug Interactions)

Methadone undergoes hepatic N-demethylation by cytochrome P-450 isoforms, principally CYP3A4, CYP2B6, CYP2C19, and to a lesser extent by CYP2C9 and CYP2D6. Coadministration of methadone with inducers of these enzymes may result in more rapid methadone metabolism, and potentially, decreased effects of methadone. Conversely, administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects. Pharmacokinetics of methadone may be unpredictable when coadministered with drugs that are known to both induce and inhibit CYP enzymes. Although antiretroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir + ritonavir combination are known to inhibit some CYPs, they are shown to reduce the plasma levels of methadone, possibly due to their CYP induction activity. Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy before making a dosage adjustment.

INDICATIONS AND USAGE

1. For the treatment of moderate to severe pain not responsive to non-narcotic analgesics.
2. For detoxification treatment of opioid addiction (heroin or other morphine-like drugs).
3. For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

Note – Outpatient maintenance and outpatient detoxification treatment may be provided only by Opioid Treatment Programs (OTPs) certified by the Federal Substance Abuse and Mental Health Services Administration (SAMHSA) and registered by the Drug Enforcement Administration (DEA). This does not preclude the maintenance treatment of a patient with concurrent opioid addiction who is hospitalized for conditions other than opioid addiction and who requires temporary maintenance during the critical period of his/her stay, or of a patient whose enrollment has been verified in a program which has been certified for maintenance treatment with methadone.

CONTRAINDICATIONS

Methadone is contraindicated in patients with a known hypersensitivity to methadone hydrochloride or any *other ingredient in METHADOSE® Oral Tablets.*

Methadone is contraindicated in any situation where opioids are contraindicated such as: patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings), and in patients with acute bronchial asthma or hypercarbia.

Methadone is contraindicated in any patient who has or is suspected of having a paralytic ileus.

WARNINGS

Respiratory Depression, Incomplete Cross-Tolerance, and Iatrogenic Overdose

Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly during the initial dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation or dose titration.

Patients tolerant to other opioids may be incompletely tolerant to methadone. Incomplete cross-tolerance is of particular concern for patients tolerant to other mu-opioid agonists who are being converted to treatment with methadone, thus making determination of dosing during opioid treatment conversion complex. Deaths have been reported during conversion from chronic, high-dose treatment with other opioid agonists. Therefore, it is critical to understand the pharmacokinetics of methadone when converting patients from other opioids (see DOSAGE AND ADMINISTRATION, Table 1, for appropriate conversion schedules). A high degree of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise.

Respiratory depression is of particular concern in elderly or debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Methadone should be administered with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, and CNS depression or coma. In these patients, even usual therapeutic doses of methadone may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. Alternative, non-opioid analgesics should be considered, and methadone should be used at the lowest effective dose and only under careful medical supervision.

Cardiac Conduction Effects

Laboratory studies, both *in vivo* and *in vitro*, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher dose treatment (> 200 mg/day). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. In most of the cases seen of typical maintenance doses, concomitant medications and/or clinical conditions such as hypokalemia were noted as contributing factors. However, the evidence strongly suggests that methadone possesses the potential for adverse cardiac conduction effects in some patients.

Methadone should be administered with particular caution to patients already at risk for development of prolonged QT interval (e.g., cardiac hypertrophy, concomitant diuretic use, hypokalemia, hypomagnesemia). Careful monitoring is recommended when using methadone in patients with a history of cardiac conduction abnormalities, those taking medications affecting cardiac conduction, and in other cases where history or physical exam suggest an increased risk of dysrhythmia. QT prolongation has also been reported in patients with no prior cardiac history who have received high doses of methadone. Patients developing QT prolongation while on methadone treatment should be evaluated for the presence of modifiable risk factors, such as concomitant medications with cardiac effects, drugs which might cause electrolyte abnormalities, and drugs which might act as inhibitors of methadone metabolism. For use of methadone to treat pain, the risk of QT prolongation and development of dysrhythmias should be weighed against the benefit of adequate pain management and the availability of alternative therapies.

Methadone treatment for analgesic therapy in patients with acute or chronic pain should only be initiated if the potential analgesic or palliative care benefit of treatment with methadone has been considered to outweigh the risk of QT prolongation that has been reported with high doses of methadone.

The use of methadone in patients already known to have a prolonged QT interval has not been systematically studied.

In using methadone an individualized benefit to risk assessment should be carried out and should include evaluation of patient presentation and complete medical history. For patients judged to be at risk, careful monitoring of cardiovascular status, including QT prolongation and dysrhythmias and those described previously should be performed.

Misuse, Abuse, and Diversion of Opioids

Methadone is a mu-opioid opioid with an abuse liability similar to that of morphine and is a Schedule II controlled substance. Methadone, like morphine and other opioids used for analgesia, has the potential for being abused and is subject to criminal diversion.

Methadone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing Methadose in situations where the clinician is concerned about an increased risk of misuse, abuse, or diversion.

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Other CNS Depressants

Patients receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics or other CNS depressants (including alcohol) concomitantly with methadone may experience respiratory depression, hypotension, profound sedation, or coma (see PRECAUTIONS).

Interactions with Alcohol and Drugs of Abuse

Methadone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression. Deaths associated with illicit use of methadone frequently have involved concomitant benzodiazepine abuse.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, opioids produce effects which may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution, and only if it is deemed essential.

Acute Abdominal Conditions

The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Hypotensive Effect

The administration of methadone may result in severe hypotension in patients whose ability to maintain normal blood pressure is compromised (e.g., severe volume depletion).

DRUG ABUSE AND DEPENDENCE

Methadose contains methadone, a mu-agonist opioid with an abuse liability similar to other opioid agonists *and is a Schedule II controlled substance.* Methadone and other opioids used in analgesia can be abused and are subject to criminal diversion.

Abuse of methadone poses a risk of overdose and death. This risk is increased with concurrent abuse of methadone with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

"Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of lost prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. However, it should be important to note that preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Physical Dependence and Tolerance

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Methadone, like other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Intake by mothers physically dependent on opioids may also be physically dependent and may exhibit *respiratory difficulties and withdrawal symptoms (see PRECAUTIONS, Pregnancy, Labor and Delivery).*

PRECAUTIONS

General

When treating pain, methadone given on a fixed-dose schedule may have a narrow therapeutic index in certain patient populations, especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia with methadone outweigh the known potential risks of cardiac conduction abnormalities, respiratory depression, altered mental states and postural hypotension. Methadone should be used with caution in elderly and debilitated patients; patients who are known to be sensitive to central nervous system depressants, such as those with cardiovascular, pulmonary, renal, or hepatic disease; and in patients with comorbid conditions or concomitant medications which may predispose to dysrhythmias.

Selection of patients for treatment with methadone should be governed by the same principles that apply to the use of other opioids (see INDICATIONS AND USAGE). Physicians should individualize treatment in every case (see DOSAGE AND ADMINISTRATION), taking into account the high degree of interpatient variability in response to and metabolism of methadone.

Drug Interactions

In vitro results suggest that methadone undergoes hepatic N-demethylation by cytochrome P450 enzymes, principally CYP3A4, CYP2B6, CYP2C19 and to a lesser extent by CYP2C9 and CYP2D6. Coadministration of methadone with CYP inducers of these enzymes may result in a more rapid metabolism and potential for decreased effects of methadone, whereas administration with CYP inhibitors may reduce metabolism and potentiate methadone's effects. Although antiretroviral drugs such as efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir + ritonavir combination are known to inhibit CYPs, they are shown to reduce the plasma levels of methadone, possibly due to their CYP induction activity. Therefore, drugs administered concomitantly with methadone should be evaluated for interaction potential; clinicians are advised to evaluate individual response to drug therapy.

Opioid Antagonists, Mixed Agonist/Antagonists, and Partial Agonists

As with other mu-agonists, patients maintained on methadone may experience withdrawal symptoms when given opioid antagonists, mixed agonist/antagonists, and partial agonists. Examples of such agents are naloxone, nalbuphine, pentazocine, nalbuphine, butorphanol, and buprenorphine.

Anti-Retroviral Agents

Abacavir, amprenavir, efavirenz, nelfinavir, nevirapine, ritonavir, lopinavir + ritonavir combination – Coadministration of these anti-retroviral agents resulted in increased clearance or decreased plasma levels of methadone. Methadone-maintained patients beginning treatment with these antiretroviral drugs should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly.

Didanosine and Stavudine – Experimental evidence demonstrated that methadone decreased the AUC and peak levels for didanosine and stavudine, with a more significant decrease for didanosine. Methadone disposition was not substantially altered.

Zidovudine – Experimental evidence demonstrated that methadone increased the area under the concentration-time curve (AUC) of zidovudine which could result in toxic effects.

Cytochrome P450 Inducers

Methadone-maintained patients beginning treatment with CYP3A4 inducers should be monitored for evidence of withdrawal effects and methadone dose should be adjusted accordingly. The following drug interactions were reported following coadministration of methadone with inducers of cytochrome P450 enzymes:

Rifampin – In patients well-stabilized on methadone, concomitant administration of rifampin resulted in a marked reduction in serum methadone levels and a concurrent appearance of withdrawal symptoms.

Phenytoin – In a pharmacokinetic study with patients on methadone maintenance therapy, phenytoin administration (250 mg b.i.d. initially for 1 day followed by 300 mg QD for 3 to 4 days) resulted in an approximately 50% reduction in methadone exposure and withdrawal symptoms occurred concurrently. Upon discontinuation of phenytoin, the incidence of withdrawal symptoms decreased and methadone exposure increased to a level comparable to that prior to phenytoin administration.

St. John's Wort, Phenobarbital, Carbamazepine – Administration of methadone along with other CYP3A4 inducers may result in withdrawal symptoms.

Cytochrome P450 Inhibitors

Since the metabolism of methadone is mediated primarily by CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of methadone. The expected clinical results would be increased or prolonged opioid effects. Thus, methadone-treated patients coadministered strong inhibitors of CYP3A4, such as azole antifungal agents (e.g., ketoconazole) and macrolide antibiotics (e.g., erythromycin), with methadone should be carefully monitored and dosage adjustment should be undertaken if warranted. Some selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline, fluvoxamine) may increase methadone plasma levels upon coadministration with methadone and result in increased opiate effects and/or toxicity.

Voriconazole – Repeat dose administration of oral voriconazole (400 mg q12h for 1 day, then 200 mg q12h for 4 days) increased the C_{max} and AUC of (R)-methadone by 31% and 47%, respectively, in subjects receiving a methadone maintenance dose (30 to 100 mg QD). The C_{max} and AUC of (S)-methadone increased by 65% and 103%, respectively. Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed.

Others

Monoamine Oxidase (MAO) Inhibitors – Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving monoamine oxidase inhibitors or those who have received such agents within 14 days. Similar reactions than far have not been reported with methadone. However, if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small, incremental doses of methadone are administered over the course of several hours while the patient's condition and vital signs are under careful observation.

Desipramine – Blood levels of desipramine have increased with concurrent methadone administration.

Potentially Arrhythmogenic Agents

Extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone. Pharmacodynamic interactions may occur with concomitant use of methadone and potentially arrhythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers.

Caution should also be exercised when prescribing methadone concomitantly with drugs capable of inducing electrolyte disturbances (hypomagnesemia, hypokalemia) that may prolong the QT interval. These drugs include diuretics, laxatives, and, in rare cases, mineralocorticoid hormones.

Interactions with Alcohol and Drugs of Abuse

Methadone may be expected to have additive effects when used in conjunction with alcohol, other opioids or CNS depressants, or with illicit drugs that cause central nervous system depression. Deaths have been reported when methadone has been abused in conjunction with benzodiazepines.

Anxiety – Since methadone as used by tolerant patients at a constant maintenance dosage does not act as a tranquilizer, patients who are maintained on this drug will react to life problems and stresses with the same symptoms of anxiety as do other individuals. The physician should not confuse such symptoms with those of narcotic abstinence and should not attempt to treat anxiety by increasing the dose of methadone. The action of methadone in maintenance treatment is limited to the control of narcotic withdrawal symptoms and is ineffective for relief of general anxiety.

Acute Pain – *Maintenance patients on a stable dose of methadone who experience physical trauma,* postoperative pain or other acute pain cannot be expected to derive analgesia from their existing dose of methadone. Such patients should be administered analgesics, including opioids, in doses that would otherwise be indicated for non-methadone-treated patients with similar painful conditions. Due to the opioid tolerance induced by methadone, when opioids are required for management of acute pain in methadone patients, somewhat higher and/or more frequent doses will often be required than would be the case for non-tolerant patients.

Risk of Relapse in Patients on Methadone Maintenance Treatment of Opioid Addiction

Abrupt opioid discontinuation can lead to development of opioid withdrawal symptoms (see PRECAUTIONS). Presentation of these symptoms have been associated with an increased risk of susceptible patients to relapse to illicit drug use and should be considered when assessing the risks and benefit of methadone use.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and/or tolerance are not unusual during chronic opioid therapy.

If methadone is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, chronically administered methadone should not be abruptly discontinued.

Special-Risk Patients

Methadone should be given with caution and the initial dose reduced in certain patients, such as the elderly and debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions appropriate to the use of parenteral opioids should be observed and the possibility of respiratory depression should always be kept in mind.

Information for Patients

- Patients should be cautioned that methadone, like all opioids, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving or operating machinery.
- Patients should be cautioned that methadone, like other opioids, may produce orthostatic hypotension in ambulatory patients.
- Patients should be cautioned that alcohol and other CNS depressants may produce an additive CNS depression when taken with this product and should be avoided.
- Patients should be instructed to seek medical attention immediately if they experience symptoms suggestive of an arrhythmia (such as palpitations, dizziness, lightheadedness, or syncope) when taking methadone.
- Patients initiating treatment with methadone for opioid dependence should be reassured that the dose of methadone will "hold" for longer periods of time as treatment progresses.
- Patients seeking to discontinue methadone maintenance treatment of opioid dependence should be apprised of the high risk of relapse to illicit drug use associated with discontinuation of methadone maintenance treatment.
- Patients should be instructed to keep methadone in a secure place out of the reach of children and other household members. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients and their caregivers should be advised to discard unused methadone in such a way that individuals other than the patient for whom it was originally prescribed will not come in contact with the drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis – The results of carcinogenicity assessment in B6C3F1 mice and Fischer 344 rats following dietary administration of two doses of methadone HCl have been published. Mice consumed 15 mg/kg/day or 60 mg/kg/day methadone for two years. These doses were approximately 0.6 and 2.5 times a human daily oral dose of 120 mg/day on a body surface area basis (mg/m²). There was a significant increase in pituitary adenomas in female mice treated with 15 mg/kg/day but not with 60 mg/kg/day. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in male rats. Due to decreased food consumption in males at the high dose, male rats consumed 16 mg/kg/day and 28 mg/kg/day of methadone for two years. These doses were approximately 1.3 and 2.3 times a human daily oral dose of 120 mg/day, based on body surface area comparison. In contrast, female rats consumed 46 mg/kg/day or 88 mg/kg/day for two years. These doses were approximately 3.7 and 7.1 times a human daily oral dose of 120 mg/day, based on body surface area comparison. Under the conditions of the assay, there was no clear evidence for a treatment-related increase in the incidence of neoplasms in either male or female rats.

Mutagenesis – There are several published reports on the potential genetic toxicity of methadone. Methadone tested negative in tests for chromosome breakage and disjunction and sex-linked recessive lethal gene mutations in germ cells of Drosophila using feeding and injection procedures. In contrast, methadone tested positive in the *in vivo* mouse dominant lethal assay and the *in vivo* micronucleus spermatogonial chromosome aberration test. Additionally, methadone tested positive in the *E. coli* DNA repair system and *Neurospora crassa* and mouse lymphoma forward mutation assays.

Fertility – Reproductive function in human males may be decreased by methadone treatment. Reductions in ejaculate volume and seminal vesicle and prostate secretions have been reported in methadone-treated individuals.

In addition, reductions in serum testosterone levels and sperm motility, and abnormalities in sperm morphology have been reported. Published animal studies provide additional data indicating that methadone treatment of males can alter reproductive function. Methadone produces a significant regression of sex accessory organs and testes of male mice and rats. Additional data have been published indicating that methadone treatment of male rats (once a day for three consecutive days) increased embryolethality and neonatal mortality. Examination of uterine contents of methadone-naïve female mice bred to methadone-treated mice indicated that methadone treatment produced an increase in the rate of preimplantation deaths in all post-meiotic stages.

Pregnancy

Teratogenic Effects. *Pregnancy Category C* – There are no controlled studies of methadone use in pregnant women that can be used to establish safety. However, an expert review of published data on experiences with methadone use during pregnancy by the Teratogen Information System (TERIS) concluded that maternal use of methadone during pregnancy as part of a supervised, therapeutic regimen is unlikely to pose a substantial teratogenic risk (quantity and quality of data assessed as "limited to fair"). However, the data are insufficient to state that there is no risk (TERIS, last reviewed October, 2002). Pregnant women involved in methadone maintenance programs have been reported to have significantly improved prenatal care leading to significantly reduced incidence of obstetric and fetal complications and neonatal morbidity and mortality *when compared to women using illicit drugs. Several factors complicate the interpretation of investigations* of the children of women who take methadone during pregnancy. These include the maternal use of illicit drugs, other maternal factors such as nutrition, infection, and psychosocial circumstances, limited information regarding dose and duration of methadone use during pregnancy, and the fact that most maternal exposure appears to occur after the first trimester of pregnancy. In addition, reported studies generally compare the benefit of methadone to the risk of untreated addiction to illicit drugs, the relevance of these findings to pain patients prescribed methadone during pregnancy is unclear.

Methadone has been detected in amniotic fluid and cord plasma at concentrations proportional to maternal plasma and in newborn urine at lower concentrations than corresponding maternal urine.

A retrospective series of 101 pregnant, opiate-dependent women who underwent inpatient opiate detoxification with methadone did not demonstrate any increased risk of miscarriage in the 2nd trimester or premature delivery in the 3rd trimester.

Several studies have suggested that infants born to narcotic-addicted women treated with methadone during all or part of pregnancy have been found to have decreased fetal growth with reduced birth weight, length, and/or head circumference compared to controls. This growth deficit does not appear to persist into later childhood. However, children born to women treated with methadone during pregnancy have been shown to demonstrate mild but persistent deficits in performance on psychometric and behavioral tests.

Additional information on the potential risks of methadone may be derived from animal data. Methadone does not appear to be teratogenic in the rat or rabbit models. However, following large doses, methadone produced teratogenic effects in the guinea pig, hamster and mouse. One published study in pregnant hamsters indicated that a single subcutaneous dose of methadone ranging from 31 to 185 mg/kg (the 31 mg/kg dose is approximately 2 times a human daily oral dose of 120 mg/day on a mg/m² basis) on day 8 of gestation resulted in a decrease in the number of fetuses per litter and an increase in the percentage of fetuses exhibiting congenital malformations described as exencephaly, craniocephalic, and "various other lesions". The majority of the doses tested also resulted in maternal death. In another study, a single subcutaneous dose of 22 to 24 mg/kg methadone (estimated exposure was approximately equivalent to a human daily oral dose of 120 mg/day on a mg/m² basis) administered on day 9 of gestation in mice also produced exencephaly in 11% of the embryos. However, no effects were reported in rats and rabbits at oral doses up to 40 mg/kg (estimated exposure was approximately 3 and 6 times, respectively, a human daily oral dose of 120 mg/day on a mg/m² basis) administered during days 6 to 15 and 6 to 18, respectively.

Nonteratogenic Effects – Babies born to mothers who have been taking opioids regularly prior to delivery may be physically dependent. Onset of withdrawal symptoms in infants is usually in the first days after birth. Withdrawal signs in the newborn include irritability and excessive crying, tremor, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. *The intensity of the* syndrome does not always correlate with the maternal dose or the duration of maternal exposure. The

duration of the withdrawal signs may vary from a few days to weeks or even months. There is no consensus on the appropriate management of infant withdrawal.

There are conflicting reports on whether SIDS occurs with an increased incidence in infants born to women treated with methadone during pregnancy.

Abnormal fetal nonstress tests (NSTs) have been reported to occur more frequently when the test is performed 1 to 2 hours after a maintenance dose of methadone in late pregnancy compared to controls.

Published animal data have reported increased neonatal mortality in the offspring of male rodents that were treated with methadone prior to mating. In these studies, the female rodents were not treated with methadone, indicating paternally-mediated developmental toxicity. Specifically, methadone administered to the male rat prior to mating with methadone-naïve females resulted in decreased weight gain in progeny after weaning. The male progeny demonstrated reduced thymus weights, whereas the female progeny demonstrated increased adrenal weights. Further, behavioral testing of these male and female progeny revealed significant differences in behavioral tests compared to control animals, suggesting that paternal methadone exposure can produce physiological and behavioral changes in progeny in this model. Other animal studies have reported that perinatal exposure to opioids including methadone alters neuronal development and behavior in the offspring. Perinatal methadone exposure in rats has been linked to alterations in learning ability, motor activity, thermal regulation, nociceptive responses and sensitivity to drugs. Additional animal data demonstrates evidence for neurochemical changes in the brains of methadone-treated offspring, including changes to the cholinergic, dopaminergic, noradrenergic and serotonergic systems. Additional studies demonstrated that methadone treatment of male rats for 21 to 32 days prior to mating with methadone-naïve females did not produce any adverse effects, suggesting that prolonged methadone treatment of the male rat resulted in tolerance to the developmental toxicities noted in the progeny. Mechanistic studies in this rat model suggest that the developmental effects of "paternal" methadone on the progeny appear to be due to decreased testosterone production. These animal data mirror *the reported clinical findings of decreased testosterone levels in human males on methadone maintenance* therapy for opioid addiction and in males receiving chronic intraspinal opioids.

Clinical Pharmacology for Pregnancy – Pregnant women appear to have significantly lower trough plasma methadone concentrations, increased plasma methadone clearance, and shorter methadone half-life than after delivery. Dosage adjustment using higher doses or administering the daily dose in divided doses may be necessary in pregnant women treated with methadone (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Methadone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used. Methadone is not recommended for obstetric analgesia because its long duration of action increases the probability of respiratory depression in the newborn. Narcotics with mixed agonist-antagonist properties should not be used for pain control during labor in patients chronically treated with methadone as they may precipitate acute withdrawal.

Nursing Mothers

Methadone is secreted into human milk. The safety of breastfeeding while taking oral methadone is controversial. At maternal oral doses of 10 to 80 mg/day, methadone concentrations from 50 to 570 mcg/L in milk have been reported, which, in the majority of samples, were lower than maternal serum drug concentrations at steady state. Peak methadone levels in milk occur approximately 4 to 5 hours after an oral dose. Based on an average milk consumption of 150 mL/kg/day, an infant would consume approximately 17.4 mcg/kg/day which is approximately 2 to 3% of the oral maternal dose. Methadone has been detected in very low plasma concentrations in some infants whose mothers were taking methadone. Women on high-dose methadone maintenance, who are already breast-feeding, should be counseled to wean breast-feeding gradually in order to prevent neonatal abstinence syndrome.

Methadone-treated mothers considering nursing an opioid-naïve infant should be counseled regarding the presence of methadone in breast milk.

Because of the potential for serious adverse reactions in nursing infants from methadone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. In patients being treated for opioid dependence, this should include weighing the risk of methadone against the risk of maternal illicit drug use.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients and caregivers should be instructed to keep methadone in a secure place out of the reach of children and to discard unused methadone in such a way that individuals other than the patient for whom it was originally prescribed will not come in contact with the drug.

Geriatric Use

Clinical studies of methadone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently compared to younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for elderly patients should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Renal Impairment

The use of methadone has not been extensively evaluated in patients with renal insufficiency.

Hepatic Impairment

The use of methadone has not been extensively evaluated in patients with hepatic insufficiency. Methadone is metabolized in the liver and patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

Gender

The use of methadone has not been evaluated for gender specificity.

ADVERSE REACTIONS

Heroin Withdrawal

During the induction phase of methadone maintenance treatment, patients are being withdrawn from heroin and may therefore show typical withdrawal symptoms, which should be differentiated from methadone-induced side effects. They may exhibit some or all of the following signs and symptoms associated with acute withdrawal from heroin or other opiates: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, goose-flesh, fever, chilliness alternating with flushing, restlessness, irritability, weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss.

Initial Administration

The initial methadone dose should be carefully titrated to the individual. Too rapid titration for the patient's sensitivity is more likely to produce adverse effects.

The major hazards of methadone are respiratory depression and, to a lesser degree, systemic hypotension. Respiratory arrest, shock, cardiac arrest, and death have occurred.

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses are advisable.

Other adverse reactions include the following:

Body as a Whole – asthenia (weakness), edema, headache

Cardiovascular – arrhythmias, bigeminal rhythms, bradycardia, cardiomyopathy, ECG abnormalities, extrasystoles, flushing, heart failure, hypotension, palpitations, phlebitis, QT interval prolongation, syncope, T-wave inversion, tachycardia, torsade de pointes, ventricular fibrillation, ventricular tachycardia

Digestive – abdominal pain, anorexia, biliary tract spasm, constipation, dry mouth, gibesitis

Hematologic and Lymphatic – reversible thrombocytopenia has been described in opioid addicts with chronic hepatitis

Metabolic and Nutritional – hypokalemia, hypomagnesemia, weight gain

Nervous – agitation, confusion, disorientation, dysphoria, euphoria, insomnia, seizures

Respiratory – pulmonary edema, respiratory depression

Skin and Appendages – pruritis, urticaria, other skin rashes, and rarely, hemorrhagic urticaria

Special Senses – hallucinations, visual disturbances

Urogenital – amenorrhea, antidiuretic effect, reduced libido and/or potency, urinary retention or hesitancy

Maintenance on a Stabilized Dose – During prolonged administration of methadone, as in a methadone maintenance treatment program, there is usually a gradual, yet progressive, disappearance of side effects over a period of several weeks. However, constipation and sweating often persist.

DRUG ABUSE AND DEPENDENCE

Methadone contains methadone, a mu-agonist opioid with an abuse liability similar to other opioid *agonists and is a Schedule II controlled substance. Methadone and other opioids used in analgesia* have the potential for being abused and are subject to criminal diversion.

Abuse

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

"Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of lost prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. However, it should be important to note that preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Physical Dependence and Tolerance

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Methadone, the other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Infants born to mothers physically dependent on opioids may also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms (see PRECAUTIONS, Pregnancy, Labor and Delivery).

OVERDOSAGE

Signs and Symptoms

Serious overdosage of methadone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal-muscle flaccidity, cold and clammy skin, and sometimes, bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment

Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. If a non-tolerant person, takes a large dose of methadone, effective opioid antagonists are available to counteract the potentially lethal respiratory depression. The physician must remember, however, that methadone is a long-acting depressant (36 to 48 hours), whereas opioid antagonists act for much shorter periods (one to three hours). The patient must, therefore, be monitored continuously for recurrence of respiratory depression and may need to be treated repeatedly with the narcotic antagonist. If the diagnosis is correct and respiratory depression is due only to overdosage of methadone, the use of other respiratory stimulants is not indicated.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or cardiovascular depression. In an individual physically dependent on opioids, the administration of the usual dose of an opioid antagonist may precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of the antagonist administered. If antagonists must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

Intravenously administered naloxone or nalmefene may be used to reverse signs of intoxication. Because of the relatively short half-life of naloxone as compared with methadone, repeated injections may be required until the status of the patient remains satisfactory. Naloxone may also be administered by continuous intravenous infusion.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

DOSAGE AND ADMINISTRATION

Methadone differs from many other opioid agonists in several important ways. Methadone's pharmacokinetic properties, coupled with high interpatient variability in its absorption, metabolism, and relative analgesic potency, necessitate a cautious and highly individualized approach to prescribing. Particular vigilance is necessary during treatment initiation, during conversion from one opioid to another, and during dose titration.

While methadone's duration of analgesic action (typically 4 to 8 hours) in the setting of single-dose studies approximates that of morphine, methadone's plasma elimination half-life is substantially longer than that of morphine (typically 8 to 59 hours vs. 1 to 5 hours). Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects. Also, with repeated dosing, methadone may be retained in the liver and then slowly released, prolonging the duration of action despite low plasma concentrations. For these reasons, steady-state plasma concentrations, and full analgesic effects, are usually not attained until 3 to 5 days of dosing. Additionally, incomplete cross-tolerance between mu-opioid agonists makes determination of dosing during opioid conversion complex.

The complexities associated with methadone dosing can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration. A high degree of "opioid tolerance" does not eliminate the possibility of methadone overdose, iatrogenic or otherwise. Deaths have been reported during conversion to methadone from chronic, high-dose treatment with other opioid agonists and during initiation of methadone treatment of addiction in subjects previously abusing high doses of other agonists.

Treatment of Pain

Optimal methadone initiation and dose titration strategies for the treatment of pain have not been determined. Published equianalgesic conversion ratios between methadone and other opioids are Imprecise, providing at best, only population averages that cannot be applied confidently to all patients. It should be noted that many commonly cited equianalgesia tables only present relative analgesic potencies of single opioid doses in non-tolerant patients, thus greatly underestimating methadone's analgesic potency, and its potential for adverse effects in repeated-dose settings. Regardless of the dose determination strategy employed, methadone is most safely initiated and titrated using small initial doses and gradual dose adjustments.

As with all opioid drugs, it is necessary to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. The following dosing recommendations should only be considered as suggested approaches to what is actually a series of clinical decisions over time in the management of the pain of each individual patient. Prescribers should always follow appropriate pain management principles of careful assessment and ongoing monitoring.

In the selection of an initial dose of Methadose, attention should be given to the following:

1. The total daily dose, potency and specific characteristics of the opioid the patient had been taking previously, if any;
2. The relative potency estimate used to calculate an equianalgesic starting methadone dose, in particular, whether it is intended for use in acute or chronic methadone dosing;
3. The patient's degree of opioid tolerance;
4. The age, general condition and medical status of the patient;
5. Concurrent medications, particularly other CNS and respiratory depressants;
6. The type, severity and expected duration of the patient's pain;
7. The acceptable balance between pain control and adverse side effects.

Initiation of Therapy in Opioid Non-Tolerant Patients

When oral methadone is used as the first analgesic in patients who are not already being treated with, and tolerant to, opioids, the usual oral methadone starting dose is 2.5 mg to 10 mg every 8 to 12 hours, slowly titrated to effect. More frequent administration may be required during methadone initiation in order to maintain adequate analgesia, and extreme caution is necessary to avoid overdosage, taking into account methadone's long elimination half-life.

Conversion from Parenteral Methadone to Oral Methadone

Conversion from parenteral methadone to oral methadone should initially use a 1:2 dose ratio (e.g., 5 mg parenteral methadone to 10 mg oral methadone).

Switching Patients to Methadone from other Chronic Opioids

Switching a patient from another chronically administered opioid to methadone requires caution due to the uncertainty of dose conversion ratios and incomplete cross-tolerance. Deaths have occurred in opioid tolerant patients during conversion to methadone.

Conversion ratios in many commonly used equianalgesic dosing tables do not apply in the setting of repeated methadone dosing. Although with single-dose administration the onset and duration of analgesic action, as well as the analgesic potency of methadone and morphine, are similar methadone's potency increases over time with repeated dosing. Furthermore, the conversion ratio between methadone and other opiates varies dramatically depending on baseline opiate (morphine equivalent) use as shown in the table below.

The dose conversion scheme below is derived from various consensus guidelines for converting chronic pain *patients to methadone from morphine. Clinicians should consult published conversion guidelines to* determine the equivalent morphine dose for patients converting from other opioids.

Table 1. Oral Morphine to Oral Methadone Conversion for Chronic Administration

Total Daily Baseline Oral Morphine Dose	Estimated Daily Oral Methadone Requirement as Percent of Total Daily Morphine Dose
< 100 mg	20% to 30%
100 to 300 mg	10% to 20%
300 to 600 mg	8% to 12%
600 mg to 1000 mg	5% to 10%
> 1000 mg	< 5 %

The total daily methadone dose derived from the table above may then be divided to reflect the intended dosing schedule (i.e., for administration every 8 hours, divide total daily methadone dose by 3).

Note – Equianalgesic methadone dosing varies not only between patients, but also within the same patient, depending on baseline morphine (or other opioid) dose. Table 1 has been included in order to illustrate this concept and to provide a safe starting point for opioid conversion. Methadone dosing should not be based solely on these tables. Methadone conversion and dose titration methods should always be individualized to account for the patient's prior opioid exposure, general medical condition, concomitant medication, and anticipated breakthrough medication use. The endpoint of titration is achievement of adequate pain relief, balanced against tolerability of opioid side effects. If a patient develops intolerable opioid related side effects, the methadone dose, or dosing interval, may need to be adjusted.

Dosage Adjustment During Pregnancy

Methadone clearance may be increased during pregnancy. Several small studies have demonstrated significantly lower trough methadone plasma concentrations and shorter methadone half-lives in women during their pregnancy compared to after their delivery. During pregnancy a woman's methadone dose may need to be increased, or their dosing interval decreased. Methadone should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Detoxification and Maintenance Treatment of Opiate Dependence

For detoxification and maintenance of opiate dependence methadone should be administered in accordance with the treatment standards cited in 42 CFR Section 8.12, including limitations on unsupervised administration.

Induction/Initial Dosing

The initial methadone dose should be administered, under supervision, when there are no signs of sedation or intoxication, and the patient shows symptoms of withdrawal. Initially, a single dose of 20 to 30 mg of methadone will often be sufficient to suppress withdrawal symptoms. The initial dose should not exceed 30 mg. If same-day dosing adjustments are to be made, the patient should be asked to wait 2 to 4 hours for further evaluation, when peak levels have been reached. An additional 5 to 10 mg of methadone may be provided if withdrawal symptoms have not been suppressed or if symptoms reappear. The total daily dose of methadone on the first day of treatment should not ordinarily exceed 40 mg. Dose adjustments should be made over the first week of treatment based on control of withdrawal symptoms at the time of expected peak activity (e.g., 2 to 4 hours after dosing). Dose adjustment should be cautious; deaths have occurred in early treatment due to the cumulative effects of the first several days' dosing. Patients should be reminded that the dose will "hold" for a longer period of time as tissue stores of methadone accumulate.

Initial doses should be lower for patients whose tolerance is expected to be low at treatment entry. Loss of tolerance should be considered in any patient who has not taken opioids for more than 5 days. Initial doses should not be determined by previous treatment episodes or dollars spent per day on illicit drug use.

For Short-Term Detoxification

For patients preferring a brief course of stabilization followed by a period of medically supervised withdrawal, it is generally recommended that the patient be titrated to a total daily dose of about 40 mg in divided doses to achieve an adequate stabilizing level. Stabilization can be continued for 2 to 3 days, after which the dose of methadone should be gradually decreased. The rate at which methadone is decreased should be determined separately for each patient. The dose of methadone can be decreased on a daily basis or at 2-day intervals, but the amount of intake should remain sufficient to keep withdrawal symptoms at a tolerable level. In hospitalized patients, a daily reduction of 20% of the total daily dose may be tolerated. In ambulatory patients, a somewhat slower schedule may be needed.

For Maintenance Treatment

Patients in maintenance treatment should be titrated to a dose at which opioid symptoms are prevented for 24 hours, drug hunger or craving is reduced, the euphoric effects of self-administered opioids are blocked or attenuated, and the patient is tolerant to the sedative effects of methadone. Most commonly, clinical stability is achieved at doses between 80 to 120 mg/day.

For Medically Supervised Withdrawal After a Period of Maintenance Treatment

There is considerable variability in the appropriate rate of methadone taper in patients choosing medically supervised withdrawal from methadone treatment. It is generally suggested that dose reductions should be less than 10% of the established tolerance or maintenance dose, and that 10 to 14-day intervals should elapse between dose reductions. Patients should be apprised of the high risk of relapse to illicit drug use associated with discontinuation of methadone maintenance treatment.

HOW SUPPLIED

METHADOSE® Oral Tablets (Methadone Hydrochloride Tablets USP):

5 mg white, scored tablets (Identified METHADOSE 5)
Bottles of 100 ..... NDC 0406-6974-34

10 mg white, scored tablets (Identified METHADOSE 10)
Bottles of 100 ..... NDC 0406-3454-34

Keep tightly closed. Dispense in a tight, light-resistant container. Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

tyco Healthcare

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Mallinckrodt

Mallinckrodt Inc.
St. Louis, MO 63134, U.S.A.

Rev 120505 rr/vi10

PATIENT INFORMATION
METHADOSE® ORAL TABLETS
METHADONE HYDROCHLORIDE TABLETS USP
5 mg, 10 mg

WARNINGS:

Keep Methadose out of the reach of children. Accidental overdose by a child is a medical emergency and can result in death. If a child accidentally takes Methadose, get emergency help right away.

Do not take a higher dose of Methadose or take it more often than prescribed. This can lead to an overdose and possible death.

Read the Patient Information that comes with Methadose before you take it and each time you get a new prescription. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment. Share the important information in this leaflet with members of your household.

What is the Most Important Information I Should Know About Methadose?

- **Methadose can cause life-threatening breathing problems** which can lead to death. These problems are more likely to happen when Methadose is first started or is someone who is not already taking other narcotic (opioid) pain medicines.
- Breathing problems from Methadose may not happen right away after taking a dose. Serious breathing problems will happen a while after you take a dose, even after pain has returned. It is very important that you take Methadose exactly as your doctor has prescribed. Talk to your doctor about your pain. Your doctor can decide if your Methadose dose needs to be changed.
- **Methadose can cause life-threatening heart beat problems** that can lead to death. Most heart beat problems have happened in people using large doses of Methadose for pain treatment. Some heart beat *problems have happened in people using smaller doses of Methadose for treatment of narcotic drug* addiction.

What is Methadose?

Methadose is a prescription medicine that contains methadone, which is a narcotic pain medicine similar to morphine. Methadose is a federally controlled substance (CII) because it is a strong opioid pain medicine that can be abused by people who abuse prescription medicines or street drugs.

- **Prevent theft and misuse. Keep your Methadose tablets in a safe place to protect them from theft.** Never give Methadose to anyone else even if they have the same symptoms you have. It may harm them and even cause death. Selling or giving away this medicine is dangerous and against the law.

Methadose is used:

1. to treat moderate to severe pain in people that do not respond to non-narcotic pain medicines;
2. to control withdrawal symptoms in patients being treated for narcotic drug addiction;
3. for maintenance treatment of narcotic drug addiction along with other social and medical services. Stopping maintenance treatment of narcotic drug addiction with Methadose may result in a return to narcotic drug use.

Who Should Not Take Methadose?

Do not take Methadose if you:

- have severe asthma or severe lung problems.
- have a blockage or obstruction in your intestines.
- are allergic to methadone or anything else in Methadose. See the end of this leaflet for a complete list of ingredients.

What Should I Tell my Doctor Before I Start Taking Methadose?

Methadose may not be right for you. Before starting Methadose, tell your doctor about all your medical and mental conditions including a history of drug or alcohol abuse or addiction.

Tell your doctor if you:

- are pregnant or plan to become pregnant. Methadose may harm your unborn baby
- are breast-feeding. Methadose passes through your breast milk and may harm your baby. You should choose to use Methadose or breast-feed, but not both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening medical problems when taken with Methadose. Be especially careful about other medicines that may make you sleepy, such as other pain medicines, anti-depressant medicines, sleeping pills, anxiety medicines, antihistamines, or tranquilizers. Sometimes, the doses of certain medicines (including Methadose) may need to be changed if they are used together.

Do not take any medicine while using Methadose until you have first talked to your doctor or pharmacist. They will be able to tell you if it is safe to take other medicines while you are using Methadose.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist each time you get a new medicine.

How Should I Take Methadose?

- **Take Methadose exactly as prescribed.** Follow your doctor's directions exactly. Your doctor may change your dose based on your reactions to the medicine. Do not change your dose unless your doctor tells you to change it. Do not take a higher dose of Methadose or take it more often than prescribed. This can lead to an overdose and possibly death.
- If you take too much Methadose or overdose, call 911 or your local emergency number right away.
- Review your medical conditions regularly with your doctor to determine if you still need Methadose, or if the dose needs to be adjusted.
- When starting treatment with Methadose for narcotic drug dependence, you should be aware that your dose of Methadose will "hold" for longer periods of time as treatment goes on.
- **Stopping Methadose.** Ask your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms. You should not stop taking Methadose all at once if you have been taking it for more than a few days.
- Tell all health professionals that treat you that you take Methadose.
- After stopping treatment with Methadose, flush the unused tablets down the toilet.

What Should I Avoid While Taking Methadose?

- **Do not drive, operate heavy machinery, or do other possible dangerous activities** until you know how Methadose affects you. Methadose can make you sleepy. Ask your doctor when it is okay to do these activities.
- Do not drink alcohol while using Methadose. It may increase the chance of having dangerous side effects.
- Do not take other medicines with Methadose without first talking with your doctor.

What are the Possible Side Effects of Methadose?

- **Methadose can cause life-threatening breathing and heart problems which can lead to death. See "What is the Most Important Information I Should Know About Methadose?"**
  - **Call your doctor or get medical help right away if you:**
    - have trouble breathing
    - have extreme drowsiness and breathing slows down
    - have slow shallow breathing (little chest movement with breathing)
    - fast or slowed heartbeat
    - feel faint, very dizzy, confused, have palpitations (irregular heart beat) or any other unusual symptoms

    These can be symptoms that you have taken too much (overdose of) Methadose, or the dose is too high for you. They can also be symptoms of a serious heart reaction. These symptoms can lead to serious problems or death if not treated right away.
- **Methadose can cause your blood pressure to drop.** This can make you feel dizzy if you get up too fast from sitting or lying down.
- **Methadose can cause physical dependence.** Do not stop taking Methadose or any other opioid without first talking to your doctor. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Talk to your doctor about slowly stopping Methadose to avoid getting sick with withdrawal symptoms. Physical dependency is not the same as drug addiction.
- **For patients using Methadose for pain treatment,** there is a chance of abuse or addiction with Methadose. The chance is higher if you are or have been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental problems.

Some common side effects of Methadose are lightheadedness, dizziness, drowsiness, nausea, vomiting and sweating. Other side effects include weakness, headache, constipation, itching, and dry mouth.

Talk to your doctor about any side effects that bother you or that do not go away.

These are not all the possible side effects of Methadose. For a complete list, ask your doctor or pharmacist.

How Should I Store Methadose Tablets?

- **Keep Methadose in a safe place away from children. Accidental use by a child is a medical emergency that can result in death. If a child accidentally takes Methadose, get emergency help right away.**
- Keep Methadose at room temperature, 68° to 77°F (20° to 25°C).
- Always keep Methadose in a secure place to protect from theft.
- Dispose of any unused Methadose remaining from a prescription as soon as they are no longer needed. Unused tablets should be flushed down the toilet.

General Information About Methadose.

Medicines are sometimes prescribed for purposes other than those listed in patient information leaflet. Do not use Methadose for a condition for which it was not prescribed. Do not give Methadose to other people, even if they have the same symptoms you have. Methadose can harm other people and even cause death. Sharing Methadose is against the law.

This leaflet summarizes the most important information about Methadose. If you would like more information, talk with your doctor. You can also ask your pharmacist or doctor for information about Methadose that is written for healthcare professionals, or you can visit www.Mallinckrodt.com or call 1-888-744-1414, option 2, then 1 between the hours of 7am and 5pm CST.

What are the Ingredients in Methadose?

Active Ingredient: methadone hydrochloride USP

Inactive Ingredients: dibasic calcium phosphate USP, microcrystalline cellulose NF, magnesium stearate NF, colloidal silicon dioxide NF, pregelatinized starch NF, and stearic acid NF.

SPECIMEN

CII

METHADONE HYDROCHLORIDE
USP POWDER

FOR ORAL USE ONLY

CONDITIONS FOR DISTRIBUTION AND USE OF METHADONE PRODUCTS

Code of Federal Regulations, Title 21, Sec. 291. 505

METHADONE PRODUCTS WHEN USED FOR THE TREATMENT OF NARCOTIC ADDICTION IN DETOXIFICATION OR MAINTENANCE PROGRAMS, SHALL BE DISPENSED ONLY BY APPROVED HOSPITAL PHARMACIES, APPROVED COMMUNITY PHARMACIES AND BY MAINTENANCE PROGRAMS APPROVED BY THE FOOD AND DRUG ADMINISTRATION AND THE DESIGNATED STATE AUTHORITY.

APPROVED MAINTENANCE PROGRAMS SHALL DISPENSE AND USE METHADONE IN ORAL FORM ONLY AND ACCORDING TO THE TREATMENT REQUIREMENTS STIPULATED IN THE FEDERAL METHADONE REGULATIONS (21 CFR 291.505).

FAILURE TO ABIDE BY THE REQUIREMENTS IN THESE REGULATIONS MAY RESULT IN CRIMINAL PROSECUTION, SEIZURE OF THE DRUG SUPPLY, REVOCATION OF THE PROGRAM APPROVAL AND INJUNCTION PRECLUDING OPERATION OF THE PROGRAM.

DESCRIPTION

Methadone Hydrochloride is a white powder. It is chemically named 6-dimethylamino-4, 4-diphenyl-3-heptanone hydrochloride.

ACTIONS

Methadone hydrochloride is a synthetic narcotic analgesic with multiple actions quantitatively similar to those of morphine, the most prominent of which involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation, detoxification or maintenance in narcotic addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

When administered orally, methadone is approximately one-half as potent as when given parenterally. Oral administration results in a delay of the onset, a lowering of the peak, and an increase in the duration of analgesic effect.

METHADONE HYDROCHLORIDE

INDICATIONS

1. Detoxification treatment of narcotic addiction (heroin or other morphine-like drugs).

2. Maintenance treatment of narcotic addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

NOTE:

If methadone is administered for treatment of heroin dependence for more than three weeks, the procedure passes from treatment of the acute withdrawal syndrome (detoxification) to maintenance therapy. Maintenance treatment is permitted to be undertaken only by approved methadone programs. This does not preclude the maintenance treatment of an addict who is hospitalized for medical conditions other than addiction and who requires temporary maintenance during the critical period of his stay or whose enrollment has been verified in a program which has approval for maintenance treatment with methadone.

CONTRAINDICATION

Hypersensitivity to methadone.

WARNINGS

Methadone hydrochloride powder is for oral administration only and is used in the preparation of a liquid by dissolving the powder in an appropriate vehicle. This preparation must not be injected. It is recommended that methadone hydrochloride liquid preparation, if dispensed, be packaged in child-resistant containers and kept out of reach of children to prevent accidental ingestion.

Methadone hydrochloride, a narcotic, is a Schedule II controlled substance under the Federal Controlled Substances Act. Appropriate security measures should be taken to safeguard stocks of methadone against diversion.

DRUG DEPENDENCE

METHADONE CAN PRODUCE DRUG DEPENDENCE OF THE MORPHINE TYPE AND, THEREFORE, HAS THE POTENTIAL FOR BEING ABUSED. PSYCHIC DEPENDENCE, PHYSICAL DEPENDENCE, AND TOLERANCE MAY DEVELOP UPON REPEATED ADMINISTRATION OF METHADONE, AND IT SHOULD BE PRESCRIBED AND ADMINISTERED WITH THE SAME DEGREE OF CAUTION APPROPRIATE TO THE USE OF MORPHINE.

Interaction with Other Central Nervous System Depressants:

Methadone should be used with caution and in reduced dosage in patients who are concurrently receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, tricyclic anti-depressants, and other C.N.S. depressants (including alcohol). Respiratory depression, hypotension, and profound sedation or coma may result.

Anxiety:

Since methadone, as used by tolerant subjects at a constant maintenance dosage, is not a tranquilizer, patients who are maintained on this drug will react

to life problems and stresses with the same symptoms of anxiety as do other individuals. The physician should not confuse such symptoms with those of narcotic abstinence and should not attempt to treat anxiety by increasing the dosage of methadone. The action of methadone in maintenance treatment is limited to the control of narcotic symptoms and is ineffective for relief of general anxiety.

Head Injury and Increased Intracranial Pressure:

The respiratory depressant effects of methadone and its capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of increased intracranial pressure. Furthermore, narcotics produce side-effects that may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution and only if it is deemed essential.

Asthma and Other Respiratory Conditions:

Methadone should be used with caution in patients having an acute asthmatic attack, in those with chronic obstructive pulmonary disease or cor pulmonale, and in individuals with a substantially decreased respiratory reserve, preexisting respiratory depression, hypoxia, or hypercapnia. In such patients, even usual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Hypotensive Effect:

The administration of methadone may result in severe hypotension in an individual whose ability to maintain his blood pressure has already been compromised by a depleted blood volume or concurrent administration of such drugs as the phenothiazines or certain anesthetics.

Use in Ambulatory Patients:

Methadone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Methadone, like other narcotics, may produce orthostatic hypotension in ambulatory patients.

Use in Pregnancy:

Safe use in pregnancy has not been established in relation to possible adverse effects on fetal development. Therefore, methadone should not be used in pregnant women unless, in the judgement of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS

Interaction with Pentazocine:

Patients who are addicted to heroin or who are on the methadone maintenance program may experience withdrawal symptoms when given pentazocine.

Interaction with Rifampin:

The concurrent administration of rifampin may possibly reduce the blood concentration of methadone to a degree sufficient to produce withdrawal symptoms. The mechanism by which rifampin may decrease blood concentrations of methadone is not fully understood, although enhanced microsomal drug-metabolized enzymes may influence drug disposition.

Acute Abdominal Conditions:

The administration of methadone or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Interaction with Monoamine Oxidase (MAO) Inhibitors:

Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving monoamine oxidase inhibitors or in those who have received such agents within fourteen days. Similar reactions thus far have not been reported with methadone; but if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small incremental doses are administered over the course of several hours while the patient's condition and vital signs are under careful observation.

Special-Risk Patients:

Methadone should be given with caution and the initial dose should be reduced in certain patients, such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture.

ADVERSE REACTIONS

Heroin Withdrawal:

During the induction phase of methadone maintenance treatment, patients are being withdrawn from heroin and may therefore show typical withdrawal symptoms, which should be differentiated from methadone-induced side-effects. They may exhibit some or all of the following symptoms associated with acute withdrawal from heroin or other opiates: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, gooseflesh, fever, chilliness alternating with flushing, restlessness, irritability, "sleepy yen," weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss.

Initial Administration:

Initially, the dosage of methadone should be carefully titrated to the individual. Induction too rapid for the patient's sensitivity is more likely to produce the following effects.

THE MAJOR HAZARDS OF METHADONE, AS OF OTHER NARCOTIC ANALGESICS, ARE RESPIRATORY DEPRESSION AND, TO A LESSER DEGREE, CIRCULATORY DEPRESSION. RESPIRATORY ARREST, SHOCK, AND CARDIAC ARREST HAVE OCCURRED.

The most frequently observed adverse reactions include lightheadedness,

dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses are advisable. Some adverse reactions may be alleviated in the ambulatory patient if he lies down.

Other adverse reactions include the following:

Central Nervous System - Euphoria, dysphoria, weakness, headache, insomnia, agitation, disorientation, and visual disturbances.

Gastro-Intestinal - Dry mouth, anorexia, constipation, and biliary tract spasm.

Cardiovascular - Flushing of the face, bradycardia, palpitation, faintness, and syncope.

Genito-Urinary - Urinary retention or hesitancy, antidiuretic effect, and reduced libido and/or potency.

Allergic - Pruritus, urticaria, other skin rashes, edema, and, rarely, hemorrhagic urticaria.

Maintenance on a Stabilized Dose:

During prolonged administration of methadone, as in a methadone maintenance treatment program, there is a gradual, yet progressive, disappearance of side-effects over a period of several weeks. However, constipation and sweating often persist.

DOSAGE AND ADMINISTRATION

METHADONE HYDROCHLORIDE POWDER MUST BE DISSOLVED IN AN APPROPRIATE LIQUID VEHICLE BEFORE ORAL ADMINISTRATION.

For Detoxification Treatment:

THE DRUG SHALL BE ADMINISTERED DAILY UNDER CLOSE SUPERVISION AS FOLLOWS:

A detoxification treatment course shall not exceed twenty-one days and may not be repeated earlier than four weeks after completion of the preceding course.

In detoxification, the patient may receive methadone when there are significant symptoms of withdrawal. The dosage schedules indicated below are recommended but could be varied in accordance with clinical judgment. Initially, a single oral dose of 15 to 20 mg. of methadone will often be sufficient to suppress withdrawal symptoms. Additional methadone may be provided if withdrawal symptoms are not suppressed or if symptoms reappear. When patients are physically dependent on high doses, it may be necessary to exceed these levels. Forty mg. per day in single or divided doses will usually constitute an adequate stabilizing dosage level. Stabilization can be continued for two to three days, and then the amount of methadone normally will be gradually decreased. The rate at which methadone is decreased will be determined separately for each patient. The dose of methadone can be decreased on a daily basis or at two-day intervals, but the amount of intake shall always be sufficient to keep withdrawal symptoms at a tolerable level. In hospitalized patients, a daily reduction of 20 percent of the total daily dose may be tolerated and may cause little discomfort. In ambulatory patients, a somewhat slower schedule may be

needed. If methadone is administered for more than three weeks, the procedure is considered to have progressed from detoxification or treatment of the acute withdrawal syndrome to maintenance treatment, even though the goal and intent may be eventual total withdrawal.

For Maintenance Treatment:

In maintenance treatment, the initial dosage of methadone should control the abstinence symptoms that follow withdrawal of narcotic drugs but should not be so great as to cause sedation, respiratory depression, or other effects of acute intoxication. It is important that the initial dosage be adjusted on an individual basis to the narcotic tolerance of the new patient. If such a patient has been a heavy user of heroin up to the day of admission, he may be given 20 mg. four to eight hours later or 40 mg. in a single oral dose. If he enters treatment with little or no narcotic tolerance (e.g., if he has recently been released from jail or other confinement), the initial dosage may be one-half these quantities. When there is any doubt, the smaller dose should be used initially. The patient should then be kept under observation, and, if symptoms of abstinence are distressing, additional 10 mg. doses may be administered as needed. Subsequently, the dosage should be adjusted individually, as tolerated and required, up to a level of 120 mg. daily. The patient will initially ingest the drug under observation daily, or at least six days a week, for the first three months. After demonstrating satisfactory adherence to the program regulations for at least three months, the patient may be permitted to reduce to three times weekly the occasions when he must ingest the drug under observation. He shall receive no more than a two-day take-home supply. With continuing adherence to the program's requirements for at least two years, he may then be permitted twice-weekly visits to the program for drug ingestion under observation with a three-day take-home supply. A daily dose of 120 mg. or more shall be justified in the medical record. Prior approval from state authority and the Food and Drug Administration is required for any dose above 120 mg. administered at the clinic and for any dose above 100 mg. to be taken at home. A regular review of dosage level should be made by the responsible physician, with careful consideration given to reduction of dosage as indicated on an individual basis. A new dosage level is only a test level until stability is achieved.

Special Considerations for a Pregnant Patient:

Caution shall be taken in the maintenance treatment of pregnant patients. Dosage levels shall be kept as low as possible if continued methadone treatment is deemed necessary. It is the responsibility of the program sponsor to assure that each female patient be fully informed concerning the possible risks to a pregnant woman or her unborn child from the use of methadone.

Special Limitations:

Treatment of Patients under Age Eighteen

1. The safety and effectiveness of methadone for use in the treatment of adolescents have not been proven by adequate clinical study. Special procedures are therefore necessary to assure that patients under age sixteen will not be admitted to a program and that patients between sixteen and eighteen years of age will be admitted to maintenance treatment only under limited conditions.
2. Patients between sixteen and eighteen years of age who were enrolled and

under treatment in approved programs on December 15, 1972, may continue in maintenance treatment. No new patients between sixteen and eighteen years of age may be admitted to a maintenance treatment program after March 15, 1973, unless a parent, legal guardian, or responsible adult designated by the state authority completes and signs Form FD 2635, "Consent for Methadone Treatment."

Methadone treatment of new patients between the ages of sixteen and eighteen years will be permitted after December 15, 1972, only with a documented history of two or more unsuccessful attempts at detoxification and a documented history of dependence on heroin or other morphine-like drugs beginning two years or more prior to application for treatment. No patient under age sixteen may be continued or started on methadone treatment after December 15, 1972, but these patients may be detoxified and retained in the program in a drug-free state for follow-up and aftercare.

3. Patients under age eighteen who are not placed on maintenance treatment may be detoxified. Detoxification may not exceed three weeks. A repeat episode of detoxification may not be initiated until four weeks after the completion of the previous detoxification.

OVERDOSAGE

Symptoms:

Serious overdosage of methadone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal-muscle flaccidity, cold and clammy skin, and, sometimes, bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment:

Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. If a non-tolerant person, especially a child, takes a large dose of methadone, effective narcotic antagonists are available to counter-act the potentially lethal respiratory depression. **THE PHYSICIAN MUST REMEMBER, HOWEVER, THAT METHADONE IS A LONG-ACTING DEPRESSANT (THIRTY-SIX TO FORTY-EIGHT HOURS), WHEREAS THE ANTAGONISTS ACT FOR MUCH SHORTER PERIODS (ONE TO THREE HOURS).** The patient must, therefore, be monitored continuously for recurrence of respiratory depression and treated repeatedly with the narcotic antagonist as needed. If the diagnosis is correct and respiratory depression is due only to overdosage of methadone, the use of respiratory stimulants is not indicated.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Intravenously administered narcotic antagonists, naloxone hydrochloride, nalorphine hydrochloride, or levallorphan tartrate are the drugs of choice to reverse signs of intoxication. These agents should be given repeatedly until the patient's status remains satisfactory. The hazard that the narcotic antagonist will further depress respiration is less likely with the use of naloxone.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

NOTE: IN AN INDIVIDUAL PHYSICALLY DEPENDENT ON NARCOTICS, THE ADMINISTRATION OF THE USUAL DOSE OF A NARCOTIC ANTAGONIST WILL PRECIPITATE AN ACUTE WITHDRAWAL SYNDROME. THE SEVERITY OF THIS SYNDROME WILL DEPEND ON THE DEGREE OF PHYSICAL DEPENDENCE AND THE DOSE OF THE ANTAGONIST ADMINISTERED. THE USE OF A NARCOTIC ANTAGONIST IN SUCH A PERSON SHOULD BE AVOIDED IF POSSIBLE. IF IT MUST BE USED TO TREAT SERIOUS RESPIRATORY DEPRESSION IN THE PHYSICALLY DEPENDENT PATIENT, THE ANTAGONIST SHOULD BE ADMINISTERED WITH EXTREME CARE AND BY TITRATION WITH SMALLER THAN USUAL DOSES OF THE ANTAGONIST.

HOW SUPPLIED

Methadone Hydrochloride is supplied in containers of 50 gm., 100 gm., 500 gm., and 1 kilogram.

Preserve in tight, light-resistant containers. Store at controlled room temperature (15° to 30°C.) (59° to 86°F.)

MALLINCKRODT

MALLINCKRODT INC.
St. Louis, Missouri 63134

JULY 1998 1274111 Printed in U.S.A

FedEx Shipment Receipt

Address Information

Ship to:	**Ship from:**
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BELTSVILLE, MD 20705 US 301-796-1200	Hazelwood, MO 63042 US 3146542312

Shipping Information
Tracking number: 796493630117
Ship date: 04/06/2009
Estimated shipping charges: 9.27

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